Journal of

CHRONIC DISEASES

VOL. 3 JUNE, 1956 NO. 6

Original Communications

DRUG EFFECTS AS MODIFIED BY AGING

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(Received for publication Nov. 12, 1955)

IT IS not surprising that clinicians and pharmacologists have long been interested in possible relationships between age and drug effects. The passing of time is obvious; the change from infancy to old age is dramatic. It seems almost ridiculous to suggest that aging should *not* affect drug responses. Yet "obvious facts" (such as "the earth is flat") have a nasty habit of turning into anachronistic nonsense, so that it behooves us to examine critically the evidence on this relationship.

Before proceeding to some of the available data, however, it might be worth while to spend a few moments discussing the problem from an *a priori* standpoint. As I have already said, few people need to be convinced that the biologic unit which is the child differs from the biologic unit which is the adult, even when we are speaking of the same individual at two different periods in his life. There are obvious differences of all sorts, even if one eliminates changes called "disease." As an individual ages, there is a continual exposure to experiences of many types—physiologic, pathologic, and psychologic. One would not be astonished to detect different "average" responses to drugs at different age levels. It is not, however, apparent why we need *necessarily* expect differences and, as it were, demand that the data fit preconceived notions. Nor is it obvious why—when differences *do* occur—the differences need be in a given direction, no matter how "reasonable" the direction may seem. For example, if one postulates that age is related to metabolic rate, and that therefore age should modify the response to drugs, the hypothesis could be correct without defining in advance whether age would be associated with increased or decreased drug response. A drug which was effective *per se* might be more potent in a person with low

Presented before the Thirty-fifth Annual Meeting of the Association for Research in Nervous and Mental Disease, New York, Dec. 9-10, 1955.

metabolic activity, whereas a drug which required transformation to an intermediary compound before any effects were produced might be *less* potent in such a person. There is also no compelling reason to rule out in advance the possibility that the *nature of the disease process* for which the drug is to be administered, or some other factor, will be the prepotent independent variable, and will override any possible differences, however real, introduced by aging.

Let us now turn to impressions obtained by scanning the journals and texts. The simplest generalization that one can make about the problem is that it is not simple and that generalizations are impossible. If one examines experimental data on animals, it is obvious that there is no comfort in store for those individuals who prefer color schemes of black and white rather than gray. For example, Unna[1] quotes four studies on the effects of atropine on animals: one investigator found that puppies were more resistant to atropine than adult dogs; another worker came up with opposite results in rabbits; the conclusions of a third worker, who used rats, tended to agree with those of the second individual; whereas a fourth investigator, also studying rats, could discern no age effects. Chen[2] found alcohol and digitalis to be more toxic to mice and rabbits, respectively, as their age increased, but in studying morphine in rats he found greatest sensitivity at both ends of the age curve, with the greatest resistance being shown by rats of intermediate age. Haag and Corbell,[3] in contrast to the experience of Chen, found digitalis just as toxic to kittens as it was to adult cats. Strychnine is said to be more poisonous for young rats than for old,[4] and arsenic deadlier for young silkworms than for older worms.[5] Whereas rabbits show a tenfold increase in susceptibility to carbon monoxide with increasing age, and rats a fifteenfold increase, guinea pigs show no change whatever as they get older.[6] Pentobarbital has been claimed to be less toxic in the adult rat than in the newborn rat,[7] and hexobarbital supposedly less toxic to old pigs.[8] The authors of the latter paper point out that of six papers, which they reviewed, on various barbiturates in various species, only one agreed with their conclusions, the others claiming greater resistance for younger animals. A seventh paper found adult male animals more resistant than young male animals, with reverse findings in females. In the endocrinologic literature, one finds that thyroxine is more toxic to old rats,[9] whereas parathyroid extract produces greater bone changes in young guinea pigs.[10]

In regard to reports on human beings, the situation is even less satisfactory, since data are harder to find. Much of the clinical "literature" on this point is in reality in the form of *ex cathedra* opinions, rather than evidence. I suppose that one of the most frequent injunctions occurring in therapeutics is the one advising "careful" administration of drugs to people at the extreme ends of the age spectrum. The implication seems to be that one need not be careful in prescribing for anyone who is not very old or very young. This attitude has a certain amount of common sense appeal to it, since by analogy one might infer that since infants and the infirm are less able to fend for themselves in general in this world, they will similarly be less resistant to the onslaughts of the overenthusiastic therapist. As the literature is examined, however, it is again hard to come up with simple advice for the physician. One finds, for example, certain authors failing to report a difference in age sensitivity to sulfa drug toxicity,[11-13] while other workers claim that one exists.[14,15] Even where people agree in principle,

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one textbook will describe "infants and children" as more tolerant to sulfanilamide than "adults,"[14] while another will differentiate "infants, children, and younger adults" from "the aged."[15] One can pair, side by side, statements that surgery is associated with a greater risk in the aged,[16] with the statement that surgery is not as great a risk as it is commonly believed to be in the aged.[17] It is sometimes possible to come up with apparently contradictory statements in the same article: one author,[18] making a case for an increased susceptibility to adverse cerebral effects after anesthesia in the aged, undermines much of his argument by presenting data which lead to the conclusion (expressed by the author) that "such episodes as are described must be extremely uncommon." The supposed increased sensitivity of elderly patients to hypnotics and opiates will be countered by a claim that in the case of the belladonna group of drugs, such patients are less likely to have adverse reactions than other adults and especially less likely than children.[19] One could go on listing other similar statements, but since the common denominator in most of the reports is a lack of data to buttress the conclusions of the authors, we shall not suffer greatly from their omission.

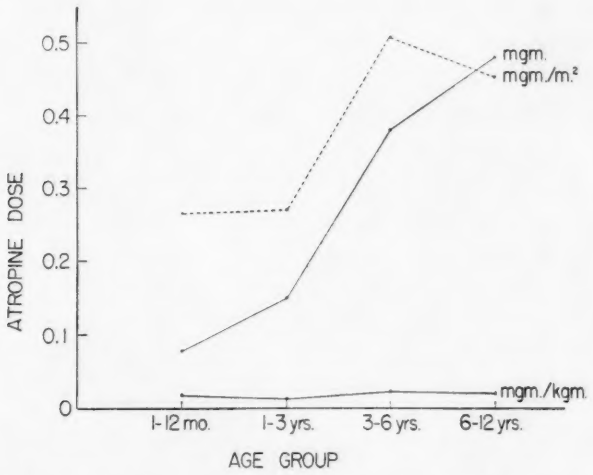

Fig. 1.—Average minimal dose of atropine required to depress salivation in children of various age groups. (After Unna.)

Instead, let us examine some actual endeavors to correlate age with drug responses in human beings. Unna[1] attempted to quantify the mean effective dose of atropine required to depress salivation in children of various age groups. The approach was to find out how much drug was required to produce the same effect in different subjects. The data are perhaps best represented by Fig. 1. It is obvious that there is a great increase (sixfold) in absolute dose with age. This increase becomes less impressive (less than twofold) if one expresses dosage on the basis of body surface, and essentially disappears if one uses body weight as a basis. Unna[1] also observes that variations in individual susceptibility to atropine are large in all age groups.

Crawford, Terry, and Rourke[20] also accumulated data bearing on the point in question. In patients ranging from infancy to adulthood, they found that

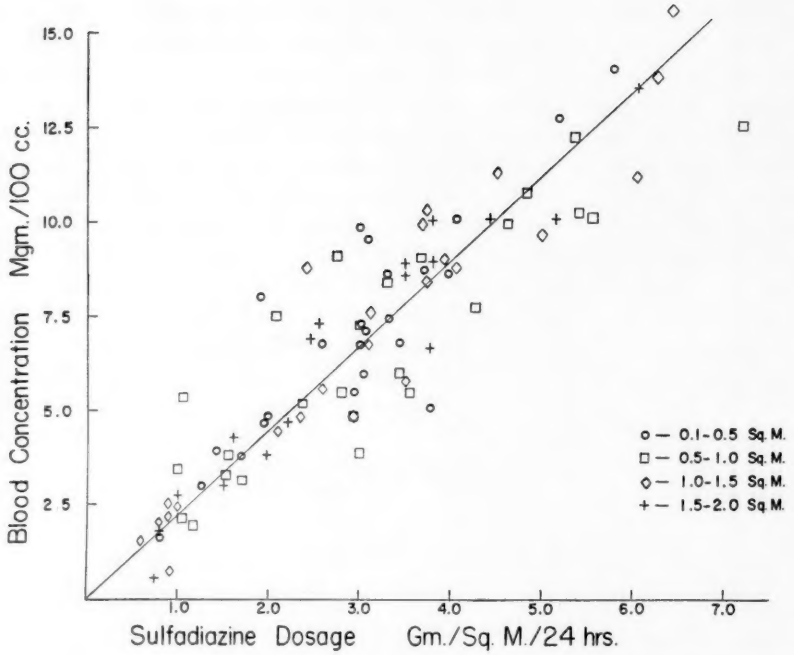

Fig. 2.—Relation between blood concentration and sulfadiazine dosage in patients of varying size. (After Crawford, Terry, and Rourke.) The symbols for surface area range in this figure comprise the following age groups: 0 (0.1-0.5 Sq. M.), infants; □ (0.5-1.0 Sq. M.), young children; ◊(1.0-1.5 Sq. M.), older children and adolescents; + (1.5-2.0 Sq. M.), adults.

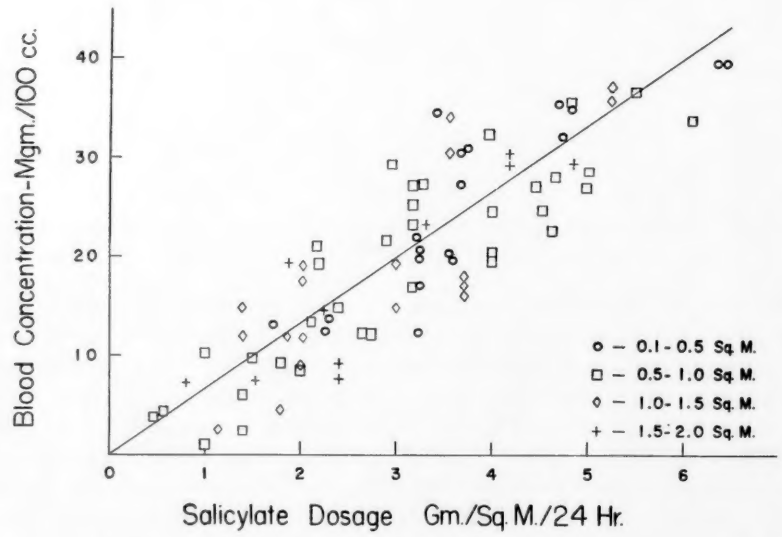

Fig. 3.—Relation between blood concentration and salicylate dosage in patients of varying size. (After Crawford, Terry, and Rourke.) The relation of the surface area symbols to the age of the patients is the same as that described for Fig. 2.

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both in the case of sulfadiazine and of aspirin, blood concentrations were directly related to dosage of drug if the drug was given on the basis of grams per square meter of body surface. In these experiments (Figs. 2 and 3), age seems to have been of no importance whatsoever in determining the response. It is true that blood concentrations of drug are not necessarily related to therapeutic effect or toxicity, but these data at least give no support to the notion that such things as absorption, distribution, etc., of drug are radically different in the age groups represented.

Another study of considerable interest is that by Bliss, Greiner, and Gold.[21] In an earlier paper, it had been stated that infants and young children were found to be considerably less susceptible to the effects of digitalis than adults. This finding was in keeping with the clinical impressions of some clinicians but at variance with the experience of certain others. On re-examining the data, however, it was found that a straight line could be obtained relating effective dose to what was essentially the square root of body weight. All differences in susceptibility previously attributed to age disappeared, although there remained a significant difference in sex response. (For those of us who consider sex a more interesting and important variable than age, these results seem particularly happy.)

At this point, it might be advisable to re-examine our problem. What is the question we are asking ourselves? Are we interested in the existence of a fundamental change in reactivity to the effects of a drug as a person gets older? If this is so, the problem becomes enormously complex. It is relatively simple to examine the performance of patients of different age groups in response to a given quantity of drug. If one does this, it is ridiculously easy to show that the same absolute quantity of drug given to a baby produces results quite different from those seen in an adult given the same quantity of drug. It should also be quite easy to show, in certain instances, that people aged 20 differ in their average response from people aged 60.

If one shifts, however, to administration of drug on the basis of body weight or body area, differences due to aging may become minimized or drop out completely. I suppose a basic point of comparison should be effective receptor site concentration for the drug in question. If a person aged 60 requires twice as much (or half as much) drug concentration at the receptor site to get a given effect as a person aged 20, this would seem to reflect a fundamental differential susceptibility to the effects of the drug. Obtaining this sort of information is really rather difficult, although one can make a good approximation by studying plasma (or plasma water) concentrations of some drugs.

To illustrate the difficulties one can get into by neglecting problems of distribution and metabolism, let us consider the case of a drug which is localized to a tremendous degree in body fat, although the organ of interest may actually be the heart or the brain. On the average, as people get older, the percentage of body weight contributed by body fat increases. Therefore the same individual weighing 150 pounds at the age of 20 and at the age of 60, and given equal amounts of the same drug at these two ages, would be receiving equal doses on the basis of body weight or body area. Yet the plasma concentrations of the drug achieved in the two instances would be quite different. A spurious differential reactivity

might thus be established. Under these same circumstances, it might also be possible to *miss* a real correlation with age. If the person at age 60 responded identically (functionally) as the person at age 20, the knowledge that the oral dose had been identical at both times would suggest that the reactivity of the individual had not altered with age. Yet the difference in blood (and brain) concentrations produced by changes in body composition with aging should have produced a lesser effect in the 60-year-old. The fact that a lesser effect was not achieved would indicate that the reactivity of his central nervous system had actually *increased* over the years. If the above examples, based on changes in distribution of drugs, seem too complex, one could describe similar difficulties in interpretation of drug responses caused by differences in drug absorption at 20 and 60 years of age.

What is obviously required is a good deal more work and a good deal less talk (in and out of print). On the basis of the data presented thus far, it seems reasonable to expect that at least some of the commonly accepted notions about the effects of age on drug responses are incorrect. For example, in studies by Keats and Beecher[22] on patients with postoperative pain, and in our own studies on patients with sleeping problems, the incidence of untoward reactions to barbiturates in the aged has certainly been unimpressive. In the latter experiments, dealing with several hundred patients of all ages, the only reaction to barbiturates at all reminiscent of the type so frequently described as "typical" of the aged was seen after the administration of secobarbital to a 17-year-old boy. If systematic attempts are made, it should be possible to amass data which would at least allow the empiric formulation of clinically useful dicta in specific situations. Even studies based on administration of a set absolute dose to patients of different ages would provide the practicing physician with rules-of-thumb which would make for more effective therapeutics.

The basic problem remains, however, of importance both theoretically and practically. It would be of interest, for example, if the variability in response to drugs increased with age. It is possible that the mean effective dose for a drug might not change particularly, but that the shape of the dose-response curve might be relatively steep or relatively flat according to age group. Presence of a relatively flat curve would increase the difficulty of defining an "optimal dose" for an age group, since the extremes (those who do not react easily or who overreact) would cover a greater spread of dosage. Such a phenomenon might explain the development of a fallacious clinical impression that *all* aged patients showed increased (or decreased) susceptibility to the effects of a drug.

It might be worthwhile to repeat at this point that age might prove to be, in many situations, a very minor determinant of drug action. There is evidence, for example, that seasonal variations of the response of rats to a barbiturate may be greater than differences between rats of varying ages at a given time of year.[23] The toxic cardiovascular effects of a drug in humans are probably more easily relatable to the state of the heart and blood vessels than to chronologic age. In some situations, as in the case of psychosis, it appears more important how long a patient has been ill rather than how old he is, in predicting response to a drug like chlorpromazine or reserpine.[24]

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I should like to plead that attempts to correlate age with response to drugs be considered only as an initial step in enlarging our understanding of the pharmacology of a given drug. If one is lucky enough to uncover a correlation between age (or weight, or body area, or *any* variable) and response to a drug, the question should then immediately be asked, "What does this correlation *mean?*" Such correlations might be of considerable importance in uncovering information about the distribution of a drug, its metabolism, excretion, or mode of action.

A few words on this point of "correlation-investigation": It is possible to demonstrate an inverse relationship between the number of letters in the name of a month and the ease of purchasing oysters in restaurants. Such a correlation implies nothing of cause and effect, and is of certain pragmatic usefulness in buying oysters. To someone vitally concerned with the problems of oyster supply, such information would be only a starting point in uncovering more important correlations. Dr. Withering's discontent with the knowledge that a concoction of 20 or more herbs was associated with relief of the symptoms of dropsy, is a classic example of the importance of asking, "What does this correlation mean?" Medicine can provide many such examples, and it is perhaps paradoxically due to the fact that correlations in medicine frequently turn out to be meaningful and not spurious that we are often tempted to accept a correlation as a basis for action, and not probe it further. For a final reminder that such a habit can lead one into untenable positions, consider this statement: "It has been conclusively demonstrated by hundreds of experiments that the beating of tom-toms will restore the sun after an eclipse."[25]

SUMMARY

Although chronologic age has been shown to be correlated with response to drugs in certain circumstances, such correlation is not inevitable nor is its nature predictable. At times increasing age seems to predispose to hyperreactivity, at times to hyporeactivity, and at times seems not to affect the magnitude of response in any significant way. The problems involved in establishing and assessing such correlations are discussed. It is suggested that the systematic collection of data bearing on this point may provide leads for important contributions to our understanding of the fate and action of drugs.

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STRUCTURAL ALTERATIONS WITH AGING IN THE NERVOUS SYSTEM

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(Received for publication Dec. 31, 1955.)

INTRODUCTION

IT IS a generally accepted concept that there is little or no multiplication of nerve cells after birth. Do the nerve cells exist as long as the organism of which they are a part? For over half a century studies have been made which indicate that there are changes in these cells which tend to lead toward a decrease in their functional ability and eventually toward the death and disappearance of many of them *before* the death of the organism. In other words, just as in an area which for some reason is becoming slowly depopulated, the community may remain for a long period as such and with its own identity while people leave or drop out one by one from the census of its inhabitants; thus nerve cells may be removed from the "cellular census" of the body.

The study of the death of nerve cells in the aging nervous system and their decrease in number from a quantitative standpoint is not at all an easy one. Indeed, there have been conflicting results in relation to the numbers of nerve cells present at various stages in several parts of the nervous system. Nevertheless, the mass of evidence at the present time does show that this loss not only is present but apparently is considerable in many regions. In certain groups of cells, as in the Purkinje cells of the cerebellum, it is seen readily.

Some of the difficulties encountered in such quantitative studies are due to the problems of counting nerve cells from section to section and others are due to the great variation from individual to individual which necessarily exists in a biologic phenomenon such as the aging process. Naturally, it is impossible to compare the nervous system of any one individual at different times, as throughout its life history, so that the factor of individual variation always enters into such studies.

In recent studies, Brody[19,20] has counted the cells in various regions of the human cerebral cortex at different ages. He finds a "patchy appearance," due to areas deficient in cells in the older cortex. These areas were scattered

Presented before the Thirty-fifth Annual Meeting of the Association for Research in Nervous and Mental Disease, New York, Dec. 9-10, 1955.

Investigation by the author of this paper has been supported by a grant from the Josiah Macy, Jr. Foundation. The author's visit to the Institut für Hirnforschung at Neustadt, Germany, for conferences with Professor Oskar Vogt, was supported in part by the Gray Pharmaceutical Company, Newton, Mass., and in part by the Josiah Macy, Jr. Foundation.

throughout the regions studied and were particularly evident in the superior temporal gyrus. Actual counts show a considerable decrease in number of cells as high in some areas as one-third or more of the original number. The cells in general are spaced more widely in senile than in young adult brains. The picture, then, in many areas of the cortex is such that low power microscopic examination permits a differentiation of sections from senile and young persons, the preparation and staining of both having been as similar as possible.

The relation between morphologic alterations and *functional* change in old age is of particular interest in the case of the nervous system. In addition to the frequently conspicuous losses in motor function in old age, the slowness of motion and the rigidity, a gradual decrease in sensitivity occurs after the third decade of life (Pearson[41]). Corbin and Gardner[23] have demonstrated a decrease in the number of dorsal root fibers corresponding to the sensory loss.

The great numbers of nerve cells which seem in individual older people to have died and disappeared probably mean a considerable loss of function, although our means of testing such loss are not very adequate at present. It is, of course, possible that in the nervous system, as in some other systems, there is a certain "reserve supply" of functioning tissue so that a loss of a moderate number of neurons may not mean a large degree of *functional* change.

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The observation, however, of the *changes* which lead toward the loss of nerve cells is not as difficult as the estimation of the degree of loss. Cells undergoing these changes are present in all older individuals and indeed can be seen to arise in some cases at a fairly early age. Again, if we use the comparison of a community, we may think of one in which there is no longer any production of new individuals. In such a community viewed from time to time there will be an increasingly larger number of older individuals and individuals showing the infirmities of age. Gradually, various members of the community will begin to drop out. In the same way with nerve cells, we see an increasing number of cells undergoing the changes of age and an increasing number which are reaching the stage of final degeneration.

Up to now we have been speaking in very general terms concerning these age changes. It is the problem in the present paper to discuss in detail the nature of the structural changes with age in the nervous system.

GROSS CHANGES

Gross changes which have been described include a certain amount of weight loss of the brain. How much of this loss of weight is due to a loss of the functional elements of the brain and how much to loss of water is not known. Also, it is not known how much of the reduction in weight may be due to actual degenerative change and how much to a physiologic process.

Other changes which may in some cases be quite striking are visible atrophy, particularly of the cerebrum, which may lead to a widening and a deepening of the sulci, and a corresponding reduction in the size of the gyri. The color of the gray matter is said to be deeper in many older brains than in young ones.

On the gross side, also, the meninges, particularly the leptomeninges, may be seen to be thickened, sometimes adherent to the brain and to one another

and difficult to pick up from the cortex. An hypertrophy of the Pacchionian granulations may also occur with old age. Patches of calcification frequently are seen in the meninges of older brains. These latter may be either senile phenomena or pathologic ones.

Atrophic changes in the cerebrum, particularly in senile dementia, frequently lead to an increase in the size of the lateral ventricles.

DEGENERATIVE CHANGES IN THE NERVE CELLS. A GENERAL SURVEY

We shall speak at first only of the changes which appear to be or which very obviously are degenerative in nature, for there are changes of quite another type which we shall discuss later. There appear to be few, if any, parts of the nervous system of man which, if studied carefully, do not reveal degenerative changes in the nerve cells with age. Studies beginning with an early investigation by Hodge (1894),[30] and followed by a large number of other workers, have shown such degeneration of nerve cells both in man and in lower animals. Mühlmann[38] described the age changes of ganglion cells of senile guinea pigs; Dolley[26] described changes in the Purkinje cells of senile dogs; Harms[28] studied the cerebrum and cerebellum of dogs; Inukai[32] found not only degenerative changes in the Purkinje cells of old rats but actual loss of cells amounting in an animal of 1,000 days to as much as 20 per cent of those which had been present at 200 days. Spiegel[49] found degenerative changes in Purkinje cells of old guinea pigs and stated that a loss as high as 40 per cent of the Purkinje cells could be seen in such animals. Andrew[1,2,4,5] described the degenerative changes in the Purkinje cells and in the cells of the cerebral cortex of the mouse and later (Andrew,[8]) in the trigeminal ganglion and spinal cord of the same type of animal. Truex and Zwemer[54] have described degeneration and loss of cells in the sensory ganglia of the cat and rat in old age.

It is natural that a number of investigators should have given attention to the question as to whether or not age changes are seen in the nerve cells in man. Indeed, several papers had described changes as of a "disintegrative" and "atrophic" nature before the beginning of the present century. Among these were Hodge (1894)[30] and Robertson and Orr (1898).[44] In more recent times Andrew,[3] and Andrew and Cardwell[13] have described degenerative changes of Purkinje cells and cells of the cerebral cortex in old age in the human subject. Truex[56] has shown a very definite process of degeneration and loss of cells in the human trigeminal ganglion with advancing age.

Riese[42] found considerable destruction in a group of brains from 18 subjects ranging from 77 to 107 years of age, but these were "mental cases." Kuhlenbeck[33] has found degenerative changes throughout the cerebral cortex of the rat, the changes being very similar to those which have been described for man. Rothschild[45] described his findings in 24 cases of individuals 66 to 100 years old at the time of death. Again, he dealt with subjects with senile psychoses. He did find widespread alterations in nerve cells in the cerebral cortex in all cases and some decrease in number.

Kuntz[34] described changes in the autonomic ganglia which are primarily degenerative in nature and include in their end stages actual loss of individual cells, together with some increase in the amount of interstitial tissue in the

ganglion. He pointed out that the same types of change which he describes are seen also in many pathologic conditions. Kuntz and Sulkin[35,36] stressed the role which the satellite cells play in some of the degenerative processes in the autonomic ganglia.

Of great interest are the findings on degenerative changes in the nerve cells of various parts of the human brain by Oskar and Cecile Vogt.[57,58] These workers and their disciples in more recent years have contributed a large amount of entirely new information in this field of which we shall have more to say later. It has been my privilege to spend some time in the laboratory of the Vogts and to see at first hand some of the evidence for their conclusions.

Having listed here the names of some of the major contributors of the studies on degenerative changes of nerve cells in lower animals and in man, we may turn now to the details of the actual changes themselves.

Change in Size, Cell Outline, and Relationship to "Satellite" Cells.—The term commonly used in referring to the change in size which comes about in the nerve cell body with advancing age in many parts of the nervous system is "shrinkage." Frequently, this is manifested in a conspicuous and striking way. Thus, where the normal or "young form" of the cell is well known and characteristic, as for example in the case of the Purkinje cell of the cerebellum with its pear-shaped body, shrinkage often leads to a great change from the original appearance. Likewise, in the pyramidal cells of the cerebral cortex, the process of shrinkage often leads to a clearly evident change in form.

In many types of nerve cells the question of whether there is a decrease in size during the process of aging is a difficult one to settle and few really quantitative studies have been done. The complicated shape of the cells, as in the case of the large motor cells of the elements of the ventral horn of the spinal cord, increases the difficulty. Among the cells of the ganglia, both autonomic and sensory, decrease in size of the cells appears as they degenerate and often appears to be a more or less "acute" process, or even to be brought about by the actions of the satellite neuroglia cells.

In many places change in size of the cells in the nervous system may be evidenced by an increase in the size of the pericellular lymphatic space, the cell which was originally of such volume as to leave very little of such space about it shrinking inward and leaving a space which on section appears as a large white vacant cavity surrounding the cell body. There is some question in many cases, of course, as to how much of this space is "real," that is, existing in the living condition, and how much is due to fixation change; but in many cases as, for instance, in the inferior olive of the medulla oblongata and in the dentate nucleus of the cerebellum, the pericellular spaces in old individuals particularly are so large and constant as to leave little doubt of their reality. Also, the larger the space the more shrunken and degenerative the contained cell appears. Spaces are present which seem to have been completely cleared of the detritus of the dead cell which once occupied them.

Decrease in size is not the only size change which may be a part of the degeneration of the nerve cell body. In cases where accumulation of relatively inert materials such as pigment and fat, of which we shall say more later on, are an accompaniment of the degenerative process, it may cause an actual increase

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in the size of the cell body or of parts of it. Such is true in the case of the accumulation and increase in size of droplets of fat in certain ganglion cells. Such also seems to be the case in some instances of accumulation of pigment. This, of course, is no more an increase in the actual living substance of the cell than it is the increase in size of an undifferentiated mesenchyme cell as it develops fat droplets, as they coalesce, and as the huge single droplet of fat is gradually developed within the substance of the cell.

Shrinkage of the cell, then, which generally is more clearly in the transverse than in the vertical diameter, brings about the loss of the smooth regularity which is seen in so many nerve cells of young individuals and often leads to a jagged and irregular outline.

DEGENERATIVE CHANGES IN THE NUCLEUS OF THE NEURON

We may now consider the nucleus of the nerve cell during the aging process. Our own studies (see above) had shown nuclear differences between young and old animals which, while they were not universally present, still were criteria of aging in a good general sense. Thus, it was noted in the Purkinje cells and in the pyramidal cells of the cerebral cortex, as also in the ganglion cells from the trigeminal ganglion, that whereas the differentiation of the nucleus from the cytoplasm seen at low power is very sharp in the young animals, it becomes increasingly less so with advancing age; and in senile animals the border line is often difficult to make out at lesser magnifications. Extension of these studies to the tissues of human subjects showed a similar difference, but the exceptions were more marked; for instance, in the cerebellum and to some extent in the cerebral cortex of individual aged human subjects, we have seen many cells with very clear vesicular nuclei standing out well from the general cytoplasm. Nevertheless, as a generalization concerning change of the nucleus with age, the statement of this decrease in differentiation between nucleus and cytoplasm holds true. It is due actually to two factors: (1) the general decrease in the amount of Nissl material in the cytoplasm and (2) a tendency to a greater basophilia of the "nuclear sap" in the nucleus in the senile nerve cell. The nucleolus in the nucleus of the nerve cell is generally paler in the old animal and sometimes shows interesting changes, some of which may be degenerative or signs of exhaustion and others which may indicate, as we shall mention later, *reactive* defensive changes.

Since many nerve cells are in the process of degeneration we may expect to find nuclei in various stages of actual death and dissolution. As long ago as 1911 Dolley described, in senile dogs, cells which seem to lack a nucleolus or even an entire nucleus, such cells being extremely distorted and staining atypically. In regard to size, there are no consistent figures for the relationship of the nucleus to the cell body with advancing age. General observations would indicate that in many cells it is smaller in the old animal than in younger animals for any given group of cells. In others again, perhaps as a reactive process, it may be unusually large.

The shape of the nucleus in the senile nerve cell is more frequently "atypical," in the sense of being elongated, somewhat irregular or angular in outline, and occasionally lobated. Again, there are many cells in which the well-rounded shape of the nucleus is retained.

In old age the position of the nucleus within the cell may be greatly altered. This seems to be due, however, not to any intrinsic tendency of the nucleus to shift position but rather to the accumulation of the inert materials in the cytoplasm. Thus, accumulations of pigment in the apical portion of the cell may force its nucleus farther toward the basal portion while accumulations in the basal portion will force a centrally located nucleus apically. This is true especially in the case of the pyramidal cells. In the case of the accumulation of vacuoles of fat, as shown clearly in the trigeminal ganglion, the nucleus is gradually pushed off far to one side just as in the case of the development of a fat cell. Here, of course, the nucleus also is distorted in shape and may last be seen as a crescent-shaped body.

CHANGES IN THE CYTOPLASM AND ITS CONSTITUENTS

Turning now to the cytoplasm of the senile nerve cell, one of the cytoplasmic components which long has been recognized as of great importance in the nerve cell is the Nissl material. The striking changes which this material undergoes under various physiologic and pathologic conditions has made it serve as a good criterion of the condition of the neuron. As we all know, in conditions such as

Fig. 1.—Giant cell of Betz from a 29-year-old man. The Nissl bodies are large and deeply stained. (Cresyl violet; ×1,495.)

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poliomyelitis and other neurologic diseases, the Nissl substance may almost or entirely disappear from the body of the nerve cell. On section of the nerve, cutting the axons of a particular group of nerve cells, there often is clear-cut chromatolysis or dissolution of this material, a fact which makes it possible to follow the course of the groups of axons. We might well expect, then, that in a profound and fundamental change such as the aging process, changes would occur also in the Nissl substance in many of the neurons of older animals. This is the type of change which does not seem to be specific for a particular group of cells but which appears to be widespread or even universal in the nervous system, both central and peripheral.

It is a striking change, since in many of the cells in youth, as in the large motor cells of the spinal cord, in the Purkinje cells, or in the pyramidal cells of the cerebral cortex, the Nissl flakes are so conspicuous (Fig. 1). In senile animals, cells of this type may be almost completely lacking in Nissl substance (Fig. 2). On the other hand, there will always be *some* which have retained a

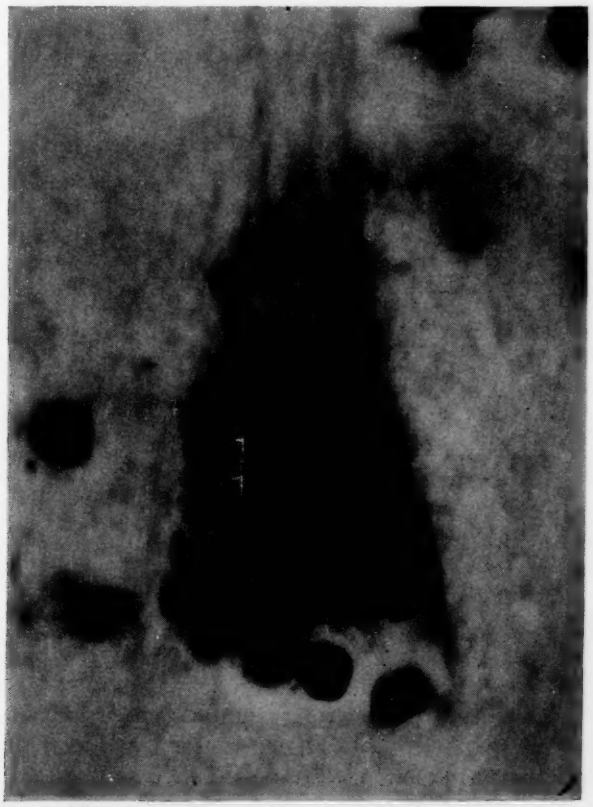

Fig. 2.—Giant cell of Betz from a 78-year-old woman. Much of the cytoplasm is devoid of Nissl substance. The smaller, dark granules on the left hand side are lipofuscin pigment. (Cresyl violet; ×1,495.)

fairly large amount of Nissl material. According to our observations, Nissl flakes may be retained in approximately the same size and architectural pattern as in youth in some cells, but their basophilia is greatly decreased as though there

might be a gradual "fading out." This we have felt to be of particular interest since the publication of the most recent findings with the electron microscope on the fine structure of the neuron. Palay and Palade are of the opinion, and show convincing evidence for their view, that the Nissl substance is composed of at least two separate components, only one of which, a minute particulate component, is responsible for the basophilic property which it exhibits. It seems, then, that the architectural structure of the flakes could be maintained while the basophilic component, the extremely minute granules scattered in the second component, a system of fine canals, were decreased in amount.

The relationship between the amount of Nissl material and the presence of inert substances—for we cannot think of the Nissl material as being inert—is of interest. In general, the amount of Nissl material seems to decrease as the pigment increases. On the other hand, cells may be seen in which there is a large accumulation of pigment in one portion with well-preserved Nissl granules in the other portion. In such cells, however, Nissl granules are decreased in total number.

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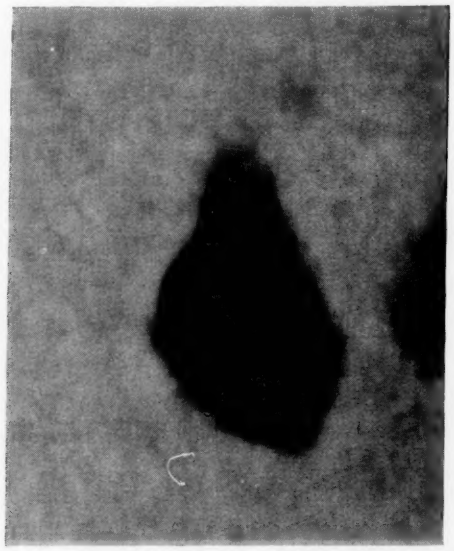

Fig. 3.—Large pyramidal cell of motor cortex in a 78-year-old woman. An accumulation of granules of lipofuscin pigment has formed a peculiar, collarlike configuration just basal to the nucleus. (Cresyl violet; ×1,495.)

The second component of the cytoplasm for discussion is the pigment. The pigment which may be considered a result of the aging process in nerve cells is that which is known as lipofuscin (Fig. 3). This lipofuscin ranges in color all the way from a relatively light golden brown through various shades of brown toward dark brown and indeed sometimes almost black in appearance. As is well known, there are certain groups of nerve cells which contain a pigment throughout all or almost all of the postnatal existence in man. This material is generally considered as entirely distinct from the age pigment. It is con-

sidered to be melanin. It is found particularly in the cells of the substantia nigra and of the locus coeruleus.

Histochemical studies on the human autonomic ganglion cells by Dr. Norman Sulkin of our department tend to confirm earlier observations on the difference between the nature of the aging pigment and the pigment found in these localized groupings of cells. The pigment of senesence does not give the reactions which are typical of melanin, such, for instance, as the bleaching by strong oxidizing agents such as potassium permanganate, hydrogen peroxide, and sodium hydroxide. Rather, the age pigment is resistant to this type of change. A number of other histochemical tests also serve to distinguish the two pigments. It may be pointed out, however, that Levi[37] states that lipofuscin, like all lipochrome pigments, consists of a nucleus of melanin surrounded by a lipoid component, so that some genetic relationship between these pigments is at least conceivable.

What, then, is the nature of the pigment which appears in increasing amounts in the cells of many parts of the nervous system with advancing age? The best evidence at present is that it is of the nature of a ceroid, similar to the insoluble pigment which is found in cirrhotic livers. While this pigment generally appears in the form of granules, it has been our experience to see it also in what appear to be vacuolar formations. In fact, as we shall see later, the amount, appearance, and distribution of the pigment vary according to the specific type of nerve cell at any given age, at least in man.

The accumulation of lipofuscin pigment in nerve cells, like many of the other changes which we are describing as occurring with advancing age, are not to be thought of as *specific* changes. In other words, pigment accumulation can and probably does occur in a variety of conditions other than that of old age; and in fact, such accumulation is one of the common "nonspecific" changes in pathologic states. To my mind, however, this does not make the gradual accumulation during the aging process any less important for the study of that process, particularly as the time of its appearance and the degree of its accumulation seem to be rather constant for special groups of nerve cells even when pathologic conditions do not complicate the picture.

I have mentioned the finding of the accumulation of fat in the trigeminal ganglion both in lower mammals and in man. Vogt[60] believes that fat can make its appearance in the nucleus and even in the nucleolus of the nerve cell. This may, of course, have to do with its later accumulation in the cytoplasm, or such accumulation may be independent of the development of fat within the nucleus. In any event, nerve cells from a number of localities in man may show large vacuoles of fatty material accumulating with advancing age. Thus, among the large pyramidal cells there are always some degenerating through fatty change in individuals of advanced age. While the picture of fatty change, with the presence of large, frequently coalescing vacuoles, is quite different from that of the accumulation of the lipofuscin pigment, there may well be some definite connection between the two which has not yet been elucidated. In fact, accumulation of fat in the nerve cell is one of the more conspicuous of the degenerative changes. According to Vogt and his disciples (see particularly Buttlar-Brentano[21]), certain groups of cells in the hypothalamus never show true fatty degeneration but do show lipofuscin accumulation (nucleus tuberomammillaris),

although other groups in close proximity to them (nucleus basalis) do show such degeneration as well as the pigment.

Another component of the neuron which, like the Nissl material, is specific for the nerve cell is the neurofibrillar complex. Many of the early investigators on nerve cells had described fine fibrils coursing through the cytoplasm of the cell. They have been described in cells of many invertebrates, of vertebrates, and of man. Nevertheless, in recent times there has been some doubt cast upon the actual existence of such neurofibrils. Since such doubt has been based, at least in part, on findings with the electron microscope, it is interesting to learn that Palay and Palade[40] believe that they have seen with very high resolution through this microscope, structures in the cytoplasm of the neuron which probably represent the neurofibrils of classical cytology.

The type of neurofibrillary change known as "Alzheimer's disease" originally was supposed to be related only to presenile dementia, but later indications are that it is fairly widespread in senile brains of human beings in general. It consists in an hypertrophy and complication of the pattern of the neurofibrillae, consisting often in the formation of whorls and baskets of these elements. Sosa[49] recently has made a study of the deposition of lipochrome (lipofuscin) pigment and correlated it with a peculiar change in the neurofibrillae which he describes as neurofibrillar degeneration. This degenerative process involves a dissociation and agglutination of neurofibrils and ends with a total dissolution of these elements. The course of the change runs parallel with the accumulation of the lipofuscin pigment.

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Turning to some of the elements which are common to all or almost all cells, we find that studies have been made upon the Golgi apparatus and mitochondria of the nerve cell with advancing age, but that such studies are up to the present very few in number. Andrew[4] found the Golgi apparatus in the Purkinje cells of young mice occurring as a large, well-developed reticular structure composed of coarse threads, while in senile animals it was represented by a mass of argentophilic granules of varying shapes and sizes, distributed irregularly in the cell. The susceptibility of the Golgi apparatus to change was shown in experimental studies by Sulkin and Kuntz[53] in which the reticular structure was altered to a granular one as a result of long electrical stimulation and induced hypertension. This work was done on the cells of autonomic ganglia. Not only did the apparatus become granular in many cells but in many others it seemed to vanish entirely.

A great deal of attention has been paid recently to the mitochondria in various types of cells, particularly since the discovery that associated with these tiny elements are many of the enzymes important in the economy of the cell. Mitochondria of the nerve cell, however, have been a somewhat vexing problem, partly on account of the difficulty of the technical procedures to demonstrate them. In fact, for a number of years during the beginning of the present century there was considerable doubt in the minds of many investigators as to whether or not the nerve cells in adult animals possessed such elements. Recently, several papers have appeared concerning the mitochondria of the nerve cell in relation to age. Hess and Lansing[29] studied the spinal ganglion cells in a group of guinea pigs ranging from newborn to senile. Their work was done with the

electron microscope. They found some mitochondria which seemed to be "degenerating" at all ages examined, and concluded that the condition of the mitochondria does not serve as a good criterion of the stage of the aging process in nerve cells. Andrew[9,10] has studied the nerve cells from several regions of the central nervous system, including the Purkinje cells of the cerebellum, the pyramidal cells of the cerebral cortex, and the large motor cells of the ventral horn of the spinal cord in the mouse, using pedigreed animals of the C-57 Black stock. Our findings include a fairly consistent type of change from a predominence, in the younger animals, of the long, filamentous or long rodlike type of mitochondrion in these three types of cells to a short rod and granular type, frequently even spheroidal or beadlike in form, in the cells of the senile mice. These studies are continuing.

We have discussed the salient changes which have been seen by various investigators in relation to the size, shape, and outline of the nerve cell body, in relation to the characteristics of the nucleus and nucleolus, and in relation to the cytoplasm and its various components including Nissl material, pigment, fat, neurofibrillae, Golgi apparatus, and mitochondria. We turn now to a consideration of the processes of the nerve cell, the elongated extensions of its cytoplasm which we know as the dendrites, and the axons. It will be recalled that of these, the axon is the more specialized and that the dendrites partake more of the characteristics of the cell body. Nissl material and even Golgi apparatus extend part way out into the dendrites. Mitochondria, on the other hand, are found both in the axon and dendrites.

In regard to quantitative studies on the numbers of axons, or actually the number of nerve fibers in given nerves or nerve roots, some of the same difficulties occur as in relation to the quantitative studies on the number of nerve cells at different ages. Corbin and Gardner[23] have shown a decrease in the number of dorsal root fibers with advancing age after the third decade in man.

There appears to be an increasing complexity of form, with the appearance of new processes, i.e., short dendrites scattered over many parts of the surface of the cell with increasing age. This, to begin with, is not a "senile" phenomenon since it may begin fairly early in life. Conti[22] has shown that in the sympathetic ganglion cells of the heart this complication in form occurs in early adult life, while after fifty years it seems to cease and, in fact, there appears to be a slight regression in volume of the cell and in richness of the processes in old age. A morphologic complication of the nerve cells is reported in the submucous and intermuscular plexuses of Meissner and Auerbach in the gastrointestinal tract of man, the process apparently continuing up through middle age, according to Borsello and Cavazzana.[18] Levi[37] cites a number of Italian workers who have found increasing complexity with age in the processes of cells of the autonomic system. In some cases this increasing complexity seems to be correlated with the degree of accumulation of pigment. Thus, for example, in the ciliary ganglion where no pigment accumulates even at a late age, the number of prolongations remains constant even in advanced age.

In many mammals such as the ox, sheep, and the goat, many "polydendritic" cells are found in old specimens. Such cells have been particularly well demonstrated in the fascia dentata. There is a marked new formation of delicate short

branches arising from all parts of the surface of the cell body. It would seem that at least part of this formation of new processes is concerned with an increase in the surface of the neuron which may help to compensate for the poor supply of tissue fluid or blood in the senile animal. On the other hand, according to Truex, cells with aberrant processes in the trigeminal ganglion probably represent degenerate neurons. Such atypical cells may be found here in varying numbers at all ages, even in normal ganglia; however, they are more common in old age. A curious phenomenon of end-bulb formation on the ends of certain of the dendritic processes is also seen in senility, according to Truex.[54] We have seen a thickening and vacuolization in dendrites of some Purkinje cells in aged mice.

"SPECIFICITY" OF THE AGE CHANGES IN PARTICULAR GROUPS OF NERVE CELLS

As we survey the broad general field of the literature on the study of age changes, including that which comes to us from the early workers in the field and that which is the product of more recent years of work in this country and abroad, we are impressed not only with the occurrence of a number of changes which appear to be common to all groups of nerve cells with advancing age, but also with the very interesting phenomenon of *specificity* of aging among different groups of nerve cells. This is a specificity in time of onset of the visible aging process, in the degree to which the process attains, and even in the *type* of change occurring as a result of senescence in different tribes or "species" of nerve cells. Let us consider a few examples of this phenomenon of specificity by enumeration of the changes which are known to occur in particular groups of cells.

In the large motor cells of the ventral horn of the spinal cord, *pigment accumulation* is a noteworthy phenomenon. While this pigment accumulation is widespread in the nervous system, it does vary considerably in its degree, that is, in the number of cells involved and in the severity of the involvement of individual cells from one part of the nervous system to another. In the large motor cells it has been found by Andrew[8] that there is no pigment in these cells in mice 40 days old, and pigment in less than 5 per cent of the cells in animals of middle age (312 days). In senile mice the accumulation of yellowish-brown pigment in the motor cells was conspicuous in every case, and the majority of the cells in old animals had half or more of the volume of the cytoplasm filled with pigment, while practically every cell showed some of this material. This work on experimental animal material is in agreement with earlier work done on human autopsy material by a number of authors including Nonne,[39] Sander,[47] Fluegel,[27] and Stern.[51] For the rest, the motor cells show the general changes which we have described as being common for many cell groups such as decrease in Nissl material, change in staining capacity of the nucleus and the nucleolus, and the greater frequency of occurrence of satellitosis. What we wish to emphasize, however, is the consistency of the development of the accumulations of the lipofuscin pigment in these cells.

In contrast to the motor cells of the spinal cord, we may next point to another group of cells which at first thought might be considered as resembling, to a fair extent, these cells—namely, the Purkinje cells of the cerebellum. These also are large efferent cells that send out impulses which, after relay by other

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groups of cells, reach the skeletal muscles of the body. Here, however, we find a totally different picture in relation to the accumulation of pigment. Accumulation of lipofuscin is a very rare phenomenon in the Purkinje cells of the human cerebellum. In examining some 60 specimens, we have seen it definitely in only one instance. In the laboratory animal, also, pigment is very seldom seen in these cells; and again, out of many specimens, we have on record only one animal in which it has been seen; and here it was present in only small amounts in individual cells. The presence of pigmented Purkinje cells in old age in even a few cases, however, indicates the tendency which they, like so many other nerve cells, have to accumulate such pigment. It seems only that the tendency is less, or perhaps that the resistance of the cell is greater. In this relation it is interesting to turn back to an early paper by Dolley.[26] In this work he brought about depression in the nerve cells of dogs and rabbits by several methods such as ether anesthesia, morphine administration, and heat. Studies also were made on Purkinje cells, the axons of which had been cut. In states of profound depression brought about experimentally, Dolley was able to witness the formation of abnormal pigmentation in the Purkinje cells. Of Dolley's view of the origin of such pigment as from within the nucleus, we need to say little. The question of the origin of pigment needs further careful study even at the present time. Here, then, in the motor horn cells and the Purkinje cells, we have two species of nerve cells which, while they resemble each other in many ways in the processes of senescence, differ radically in respect to the degree of accumulation of the "age pigment."

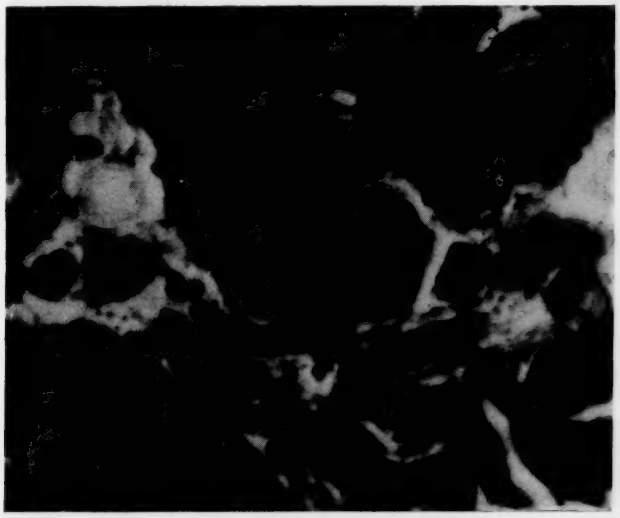

Fig. 4.—Binucleate Purkinje cell in a senile mouse, a 634-day male. Each nucleus shows its nucleolus. (×2,106.)

A striking and peculiar phenomenon among the Purkinje cells, which has been described as occurring in old age in mice and rats and in certain pathologic conditions in man, is an actual amitotic division of the nucleus (Fig. 4). In this process the nucleolus constricts and divides, the nucleus becomes horseshoe-

shaped or dumbbell-shaped, and then complete division of the nucleus takes place, giving rise to a binucleate cell. In other cases a more subtle form of division of the nucleus occurs with the appearance of a line of separation prior to the actual division of the nucleus—a formation, as it were, of an internal nuclear membrane in the central plane of the nucleus. It has been suggested[10] that this type of amitotic division, through an increase in nuclear surface, actually is a means of survival of the senile cell. We shall see later that some other parts of the nervous system show phenomena similar to this and add further evidence to the intriguing concept of a "defense reaction" against the phenomena of senescence.

A third group of cells, those of the dentate nucleus of the cerebellum, are seen in old age to contain very large accumulations of pigment which seem greatly to have affected the form of the cell and the position of the nucleus. A recent study by Höpker,[31] a student of Oskar Vogt, has concentrated on the changes in the dentate nucleus.

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In the large and conspicuous nucleus of the medulla, which we know as the inferior olivary nucleus, the pigment has a peculiar history. It seems to appear almost simultaneously in all the cells of this large nucleus at about the seventh year of life in the human being and thereafter to increase gradually until about thirty years and apparently much more slowly after thirty years. This is a striking example of early appearance and very long-term accumulation of the age pigment (Levi[37]).

In the thalamus, an interesting relationship is seen among the nuclei in relation to the time of onset and speed of the aging process as evidenced particularly by the actual loss of nerve cells. The central part of the thalamus becomes affected earliest. Here the nucleus parvocellularis begins to show a loss of cells. As the change becomes more marked in it, a similar change begins then in the nucleus mediocellularis and proceeds there. Meanwhile, the nucleus parafascicularis may not be at all affected as yet, but as the mediocellularis becomes more severely affected, the parafascicularis begins to show change. Thus, there is a very clear-cut difference in the onset and rate of aging in these adjoining nuclei of the thalamus.

The special areas of the central nervous system which contain cells heavily laden with melanin pigment, namely the substantia nigra and the locus caeruleus, also show special types of age changes. These consist in a decrease in old age in the amount of the melanin pigment present, so that in some cells it is completely lost, and the appearance within the cytoplasm, as the pigment disappears, of peculiar "Masson positive" inclusions often of great size.

The nuclei of the hypothalamus show perhaps the most impressive and striking incidence of specificity of age change seen anywhere in the nervous system. According to recent findings[21] (Buttlar-Brentano[21]), there is almost no evidence of real degenerative change in the cells of the nucleus supraopticus and of the nucleus paraventricularis.

In these two nuclei of the hypothalamus, Buttlar-Brentano states that she finds no cell destruction (Zelluntergange) whatever. Also, there is no accumulation of lipofuscin in any of the cells nor any other degenerative type of cell change except that in some single nerve cells there is a decrease of Nissl material,

accompanied by vacuolation, a decreasing mass of substance of the cell body and, after a period of hyperchromatosis of the nucleus, apparently a regression of this element. In other words, some indications of cellular degeneration are evident but no evidences of cell destruction. The curious and important finding for these cell groups is the occurrence of certain "reactive" or "defensive" phenomena which seem to be related to counteraction against the influences which lead to senescence and ultimate destruction of the nerve cell.

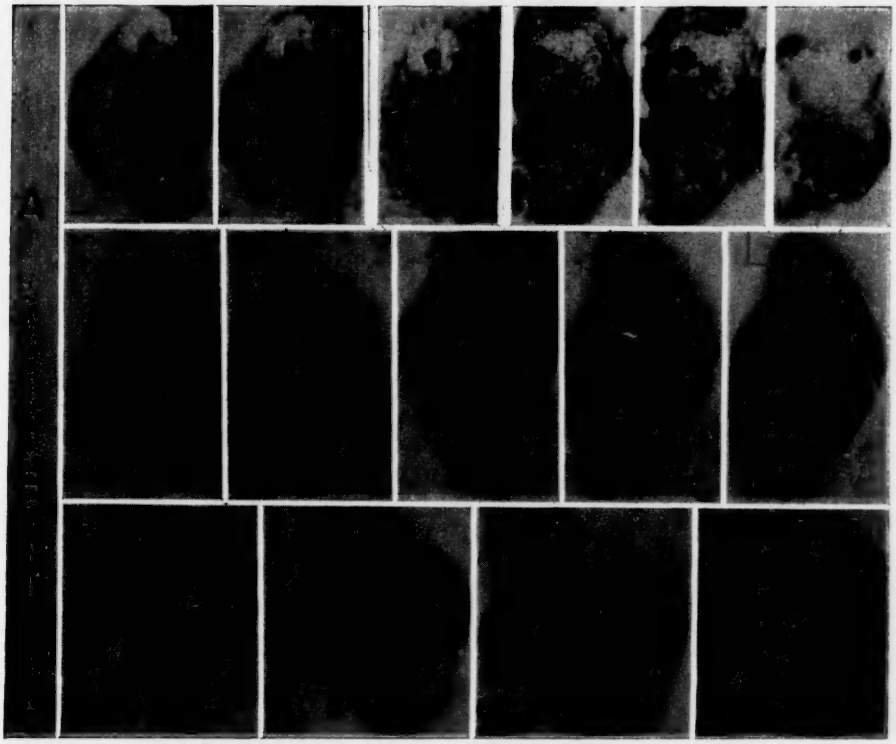

Fig. 5.—Multinucleate cells from the supraoptic nucleus of aged subjects. *A*, Binucleate cells showing differences in the two nuclei; *B*, Binucleate cell in the first two pictures, different foci of a trinucleate cell in the last three pictures; *C*, a cell with four nuclei, shown at different foci. (Approximately ×1,000.) (After Buttlar-Brentano.[21])

What are these reactive phenomena? They appear to consist in several types of changes in the cell. First, many of the cells of these nuclei in older individuals increase tremendously in size so that they become what may well be called "giant cells," having a surface area of 8 to 10 times the size which these cells have on an average in younger individuals. Second, a number of cells are seen which have two or more nuclei in the cell—multinucleate cells (Fig. 5) which, by the increased surface area of the nuclei for exchange with the cytoplasm, would be in a better position to survive the metabolic vicissitudes of old age. Third, in many cells the nucleolus, which throughout the many years of life has remained as a single element, now undergoes division and in various

cells two, three, four, and even up to six nucleoli (Fig. 6) can be found in a single nucleus. Fourth, there is frequently an increase in the basophilic properties of the nucleus, apparently due to an increase in the amount of ribonucleotide, which can bring the nucleus to a stage which resembles pycnosis but which represents,

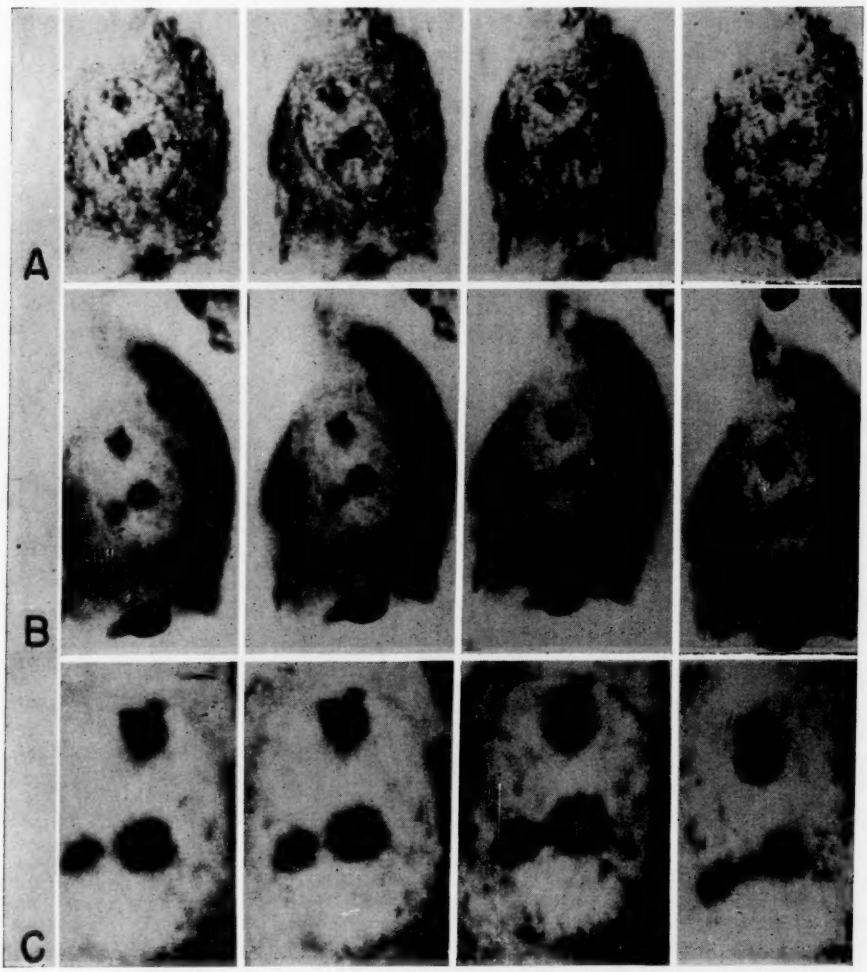

Fig. 6.—A nerve cell with multiple nucleoli (4) in the supraoptic nucleus of a senile subject. *A*, Cell stained with acid fuchsin and light green, the largest nucleolus stained red, the other three green, ×1000; *B*, same with cresyl violet stain, all nucleoli staining blue, various foci seen, ×1,000; *C*, same at ×2,000. (After Buttlar-Brentano.[21])

rather than degeneration, a type of reactive process. Buttlar-Brentano had a large amount of good material with which to work—sixty-four brains of individuals from the collection in the Institute for Brain Research of Professor Oskar Vogt. Of the 64 specimens, nineteen were from individuals ranging from 77 to 100 years of age.

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Recently, in studying the substantia nigra in some senile brain material, we have obtained what we consider good evidence of a similar reactive process in cells of this large area. The evidence for reaction here includes a tendency for the nucleus to divide (Fig. 7) and also a tendency for the nucleoli, which often are of several rather widely differing sizes to multiply (Fig. 8).

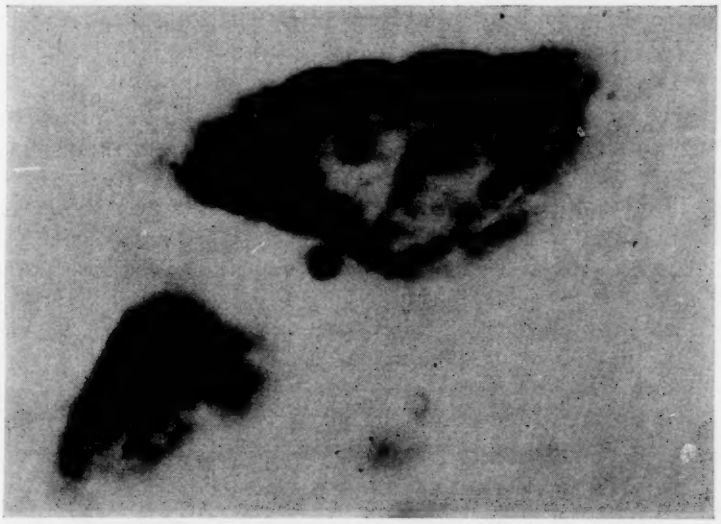

Fig. 7.—Substantia nigra of 78-year-old woman. The large cell shows a nucleus of double character, a type of amitosis which is brought about by formation of an internal partition. (Cresyl violet; ×1,495.)

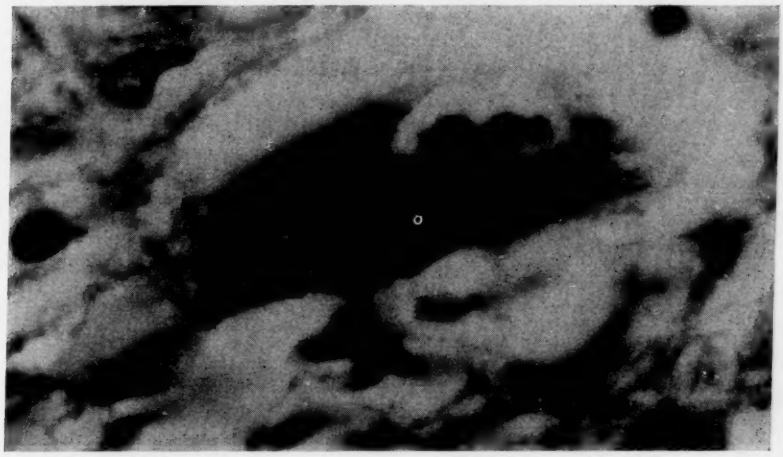

Fig. 8.—Substantia nigra of 78-year-old woman. This cell shows three nucleoli. Multiple nucleoli are very seldom seen in younger individuals. (Cresyl violet; ×1,495.)

In the cells of the "higher centers of the brain," in the gray matter which forms the cerebral cortex, as well as in the lower centers, we find definite changes with age. Balthasar[14-16] studied particularly the large pyramidal cells in the fifth layer of the area gigantopyramidalis of the human brain. The large py-

ramidal cells and the giant cells, cells of Betz, have been divided by Balthasar into two categories, namely, the centronuclear cells, in which the nucleus occupies approximately the center of the cell body, and the basonuclear cells, in which the nucleus occupies the basal portion of the cell body. In these two types of cells the location of the accumulating lipofuscin pigment is different. In the centronuclear cells it accumulates basal to the nucleus, eventually forming a large, fairly well-circumscribed mass there and tending to move the nucleus toward the apex, while in the basonuclear cells it accumulates in the apical portion of the cell, tending to move the nucleus eventually basalward.

The zone of cytoplasm in which pigment tends to accumulate has been called by Balthasar the lipophil zone of the cell. Accumulation of pigment is a marked feature of the aging process in these pyramidal cells of the cerebral cortex. It is pointed out, however, that the beginnings of this accumulation may be at a fairly early age. Thus, for instance, in a man 24 years of age, out of 196 centronuclear giant cells, 51 showed clearly some lipofuscin beginning to accumulate in the lipophil zone.

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The changes occurring in various areas of the cerebral cortex have been recognized by a number of authors. We ourselves have been struck particularly by the phenomena of increased satellitosis and what appears to be neuronocytolysis of a number of the cells (Fig. 9). In recent personal observations, we

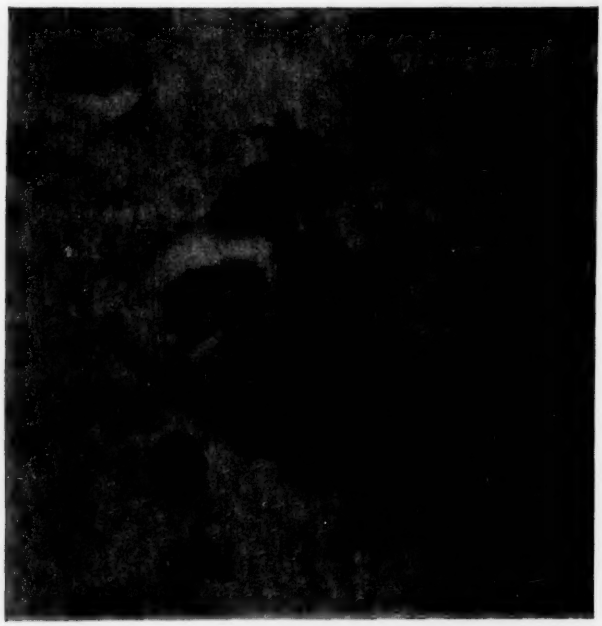
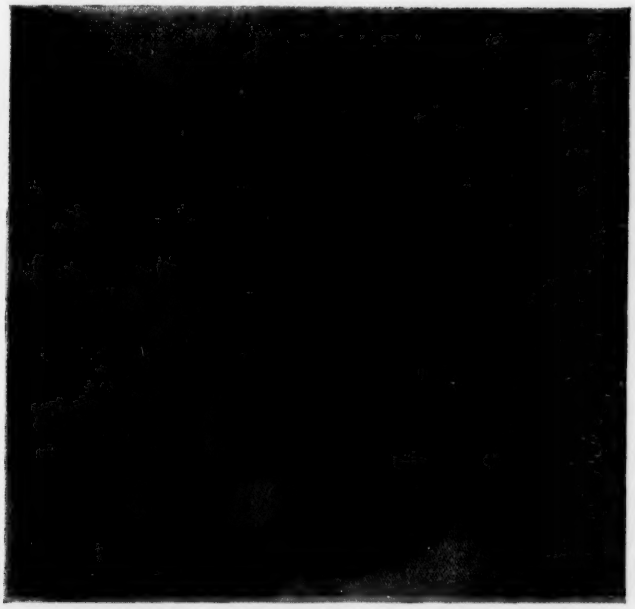
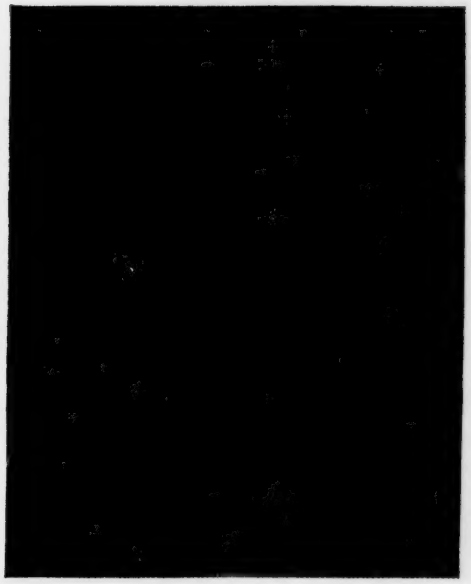


Fig. 9.—Remains of a nerve cell, probably a giant cell of Betz. Fragments of cytoplasm and groups of lipofuscin granules are seen, with a large number of satellites aiding in the lysis and disposal of this "neuronal debris," (78-year-old woman). (Cresyl violet; ×1,495.)

have been able to see for the first time also an evidence of a transfer of pigment from the nerve cell body to the satellite cell (Plate I, Fig. 10,*A*). Our observations agree well in relation to the accumulation of the lipofuscin pigment with the findings by Balthasar.

A.





B. C.

Fig. 10.—Some aspects of the accumulation of the age pigment, lipofuscin, in human nerve cells.

A, Giant cell of Betz in the motor cortex of a woman of 78 years. Small amounts of pigment are present in the nerve cell, but, significantly, one of its *satellites*, that on the right, contains prominent pigment granules. We believe that satellite cells actually remove such material, to some degree at least, from large nerve cells. (Cresyl violet; ×1,495.)

B, Cell of the inferior olive of a 29-year-old man. The pigment is scanty in amount. The nucleus and nucleolus are prominent. (Masson's stain; ×1,495.)

C, Cell of the inferior olive in a 78-year-old woman. Pigment is abundant and the nucleus is obscured. (Masson's stain; ×1,495.)

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It is interesting to note that Kuhlenbeck[33] found that increase in lipoid-containing pigment is a less prominent feature in the nerve cells of the cerebral cortex in senile rats than in those of senile man, for he witnessed frequent conspicuous accumulation of lipofuscin in the large pyramidal cells in man and very seldom in these same cells in the rat, although he states that spinal and cranial ganglion cells of the aged rat do show a rather marked increase of lipoid, and that the nerve cells of the brain stem show some accumulation also. Wilcox,[61] working with perfused material and tending to stress the minor nature of age changes found in such material, still saw a considerable accumulation of lipoid pigment in cells of various nuclei of the brain stem in the guinea pig.

In this regard it is interesting to note that Levi[37] believes that the accumulation of pigment in the nerve cells, as well as some of the other changes with age, are more marked in the human species than in other mammals.

Pursuing our search for specific types of change in cells in various parts of the nervous system, we come now to the sensory ganglia. Here we find that the type of true fatty degeneration, as described by Truex[55] and by Truex and Zwemer,[56] stands out as a conspicuous phenomenon. More work needs to be done in order to understand how widespread this phenomenon is in various of the sensory ganglia and in different species of animals; but the findings in the ganglia which have been examined show a more striking fatty change than has been seen in any other types of cells in the nervous system.

In the autonomic ganglia, on the other hand, investigators have failed to find this type of change. In fact, the cells of the autonomic ganglia seem to show chiefly the types of age change which we have described for nerve cells in general—the decrease in the Nissl material, the deposition of pigment, and degenerative changes which frequently lead to a dissolution of the cell with the occurrence of neuronophagia in moderate degree, brought about by the satellite cells of these neurons, cells which apparently correspond to the oligodendroglia of the central nervous system. Nevertheless, the phenomenon of specificity enters here also, for in the autonomic nervous system certain ganglia seem to behave differently from others. Thus, we have already mentioned the fact cited by Levi[37] that the ciliary ganglion seems surprisingly free of pigment even at an advanced age and that, apparently parallel with this lack of pigment, there is a general lack of other types of age change in this ganglion. In contrast, the superior cervical ganglion is one of the parts of the nervous system which shows the earliest changes of age and which reaches a degree of degeneration attained in few if any other parts of the system.

While such differences in the time of onset and the degree of accumulation of pigment appear to be fairly constant for the different parts of the nervous system, it is certain also that there are individual variations, and in some cases the relative times in two parts may even be reversed, as, for instance (according to Levi[37]), in the anterior horn of the spinal cord and in the cerebral cortex, where either one or the other may be precocious in the development of pigment. Again, there is a report of an individual 81 years of age in which all of the neurons of the central and of the peripheral nervous system appear to be free of pigment. Unfortunately, Levi does not cite a reference for this case, which might be of considerable interest.

SUMMARY AND CONCLUSIONS

As is true in so many other fields of scientific effort, the total picture which we now have of the aging process in the nervous system has been the result of the work of a large number of investigators working in many different laboratories and in many countries. From their efforts has developed a fairly clear picture of the slow process of change which neurons undergo through the life history of the individual. Thus, our picture of aging in the nervous system is based on many well-founded observations at the present time; and these observations are so numerous and so confirmatory of one another in many instances that we are able even to do some theorizing about the senescence of nerve cells.

The degenerative changes which we have described, particularly for the human nervous system, but also applying to other mammalian species such as the mouse, rat, and dog, present a consistent although somewhat complicated pattern. They show both a loss of material such as the Nissl substance and an accumulation of material such as the age pigment. They show changes both in the appearance of the cytoplasm and of the nuclei. They show a tendency to a change in relationship between the nerve cell and the neighboring neuroglial cells, or satellites of the neuron. They show in many cases frank degeneration and actual death of cells with their disappearance from the scene. They demonstrate also a *specificity* in the aging process in groups of nerve cells in different parts of the nervous system, in regard to time of onset, severity of change, and even type of change which occurs.

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But now, in addition to this side of the picture of the aging process in the nervous system, that of degeneration and death, we have attained to a view of an additional aspect of the aging process—one in which we see a certain amount of reaction—of defensive or compensatory change on the part of individual nerve cells. In laboratory animals Inukai[32] and Andrew[2,7,8,10] have demonstrated a process of amitotic division of the nucleus in one type of cell, the Purkinje cell of the cerebellum, and Andrew[4-6] and others have shown this process to occur in pathologic conditions in man. The extremely important work of Oskar Vogt and his disciples has indicated that a variety of definitely defensive activities occur in the nuclei of the hypothalamus with advancing age, and that these defensive activities are effective in preventing actual degeneration or death of the cells in the supraoptic and paraventricular nuclei. It is of immense interest that these reactions include division of nuclei by amitotic division as in the case of the Purkinje cells. Nucleolar reaction, the division of nucleoli, appears also to be a form of defensive activity, and makes it seem logical to look closely for phenomena involving the nucleolus when we are considering this type of change in nerve cells. It seems probable that the presence or absence of defensive changes in nerve cells will depend in different species upon different factors. Surely it appears to be different in the case of the Purkinje cells of man and of the rodent. Studies are needed also on many other parts of the nervous system, as on the substantia nigra and other areas in which there are some indications of this type of reaction.

These new developments in studies on the nervous system should be of great interest and stimulation for further investigations. They should make our role

as seekers of some means of retarding or ameliorating the aging process seem to be one which is based on firmer ground, for now we can be regarded as acting not only against the degenerative process, which is apparently part of the great scheme of nature, but also as attempting to aid a process in which the cells themselves are engaged, namely, the defense against the process of degeneration of which we are beginning to see dimly, at least, some indications in our studies on nerve cells in old age. Thus our own efforts will seem to be more in accord with those of nature.

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THE TREATMENT OF SEVERE ARTERIAL HYPERTENSION WITH PENTOLINIUM

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(Received for publication Dec. 1, 1955.)

THE drugs now in use for the treatment of arterial hypertension are aimed primarily at lowering the blood pressure. The measurement of blood pressure is notoriously variable, depending on the patient's mental and physical states and upon the amount of suggestion he receives from the physician. Moreover, the height of the blood pressure certainly does not reflect the severity of the disease in every patient. The available drugs are not specific in their effect on blood pressure, and each has other pharmacologic actions which result in the patient's discomfort. Therapeutic uncertainty must arise inevitably when so many variables are being weighed in a clinical evaluation. This was amply shown in a recent symposium in which a number of leading authorities showed little agreement as to which drug or combination of drugs should be used or which patients should be selected for treatment.[1] Each drug or combination has its champions and a comparative evaluation of regimens is most difficult.

However much the individual physician would wish to postpone the use of these agents and await either more agreement or a more perfect drug, he is not justified in doing so. Improvement of serious manifestations of severe hypertension and a prolongation of the expected life span in patients with malignant hypertension have been demonstrated with agents presently available.[2-6] Thus it is necessary for the physician to select from the variety of methods a scheme of treatment and become expert in its use.

This paper deals with the plan used at Stanford University Hospitals during the past year, especially in regard to severe hypertension.

The great majority of patients with asymptomatic high arterial blood pressures were treated without drugs or with mild sedation. If extreme nervousness accompanied the hypertension or if the hypertension seemed responsible for mild symptoms, Rauwolfia or one of its derivatives often was used in place of the traditional phenobarbital.

For those patients with severe hypertension who showed definite signs of cardiovascular damage, pentolinium tartrate† was selected because it was reported capable of producing a hypotensive response in nearly every patient and could be given orally with more uniform and lasting results than those with hexamethonium.[7-10] Because reserpine‡ was reported to potentiate the response to

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†Pentolinium tartrate was kindly suppled as Ansolysen tartrate by Wyeth, Inc.

‡Reserpine was kindly suppled as Raused by E. R. Squibb & Sons.

pentolinium and to eliminate some of the wide swings of pressure induced by the latter,[11,12] it was included in most treatment schedules. The following method is essentially that described by Professor Smirk.[3,13]

SELECTION OF PATIENTS

Eight patients who had severe hypertension resulting in definite signs of vascular or cardiac damage were selected for pentolinium treatment. All had retinal hemorrhages or exudates. Four were in congestive heart failure. All had proteinuria and three had serum creatinine levels of over 2.0 mg per 100 ml. Tests using phentolamine (Regitine) or piperoxan (Benodaine) were negative in all patients. Seven of the patients had intravenous pyelograms, and these were normal except for poor concentration of the contrast medium in Case 8.

PLAN OF TREATMENT

If the patients met the above criteria and seemed intelligent enough to carry out the regimen, the seriousness of their condition and the unpleasant effects of treatment were described to them. They were told that they would experience the feeling of a dry mouth and a loss of visual accommodation during the height of the drug effect. Male patients were advised that sexual potency would be lost during the drug administration. They were warned about the orthostatic hypotensive effect so that they might avoid situations involving prolonged standing without opportunity to sit down. They were told that any long peroid of constipation would lead to a more severe hypotensive effort and that milk of magnesia should be taken on any day in which there was no bowel movement. It was pointed out that ingestion of liquor or a heavy meal would also potentiate the drug effect. The patients were instructed to sit up during the night at a 45 degree angle with the aid of a triangular frame prop under the mattress or, if possible, by the use of a hospital-type bed. This was advocated in order to utilize the postural effect during the night. If a larger dose is given at night to overcome the antihypotensive effect of the horizontal position, there is the risk of the patient's fainting should he arise from bed.

For the beginning of treatment, the patients were usually hospitalized so that the rare causes of hypertension might be excluded, and so that the dose of pentolinium might be increased more rapidly than would be possible with less frequent observation. The pentolinium was given on an eight-hour schedule with the first dose at least one hour or preferably more before breakfast. The other doses did not conflict with meals. After an initial dose of 20 mg. three times a day, the individual dose was usually increased by 20 mg. each day until an adequate drop of pressure was achieved. Since drug retention may occur in patients with nitrogen retention, patients with an elevated concentration of urea or creatinine in the serum were treated with smaller initial doses and the dosage was increased more slowly.

Usually a larger dose was necessary to control the patients' arterial pressures during their outpatient treatment. Therefore most patients were required to attend the clinic at least three times a week until control could be re-established. Thereafter, the visits were spaced at one-or two-week intervals.

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The usual morning dose of pentolinium was administered at the beginning of each visit. The patients ate a meal approximating their usual breakfast one hour after the dose. Blood pressure determinations taken with the patients sitting and after one minute of standing were recorded every half-hour by one of the authors. Except for these interruptions, the period was one of quiet reading or talking and usually lasted four or five hours. The patients were not dismissed until the arterial pressure had reached its trough and was definitely mounting again. The best response was considered to be one in which the lowest reading obtained was 120/80 mm. Hg. Such a value would seem to insure the best control attainable without inducing too many hypotensive episodes. Had the patients been older, the 120/80 mm. Hg value probably would have been too low.

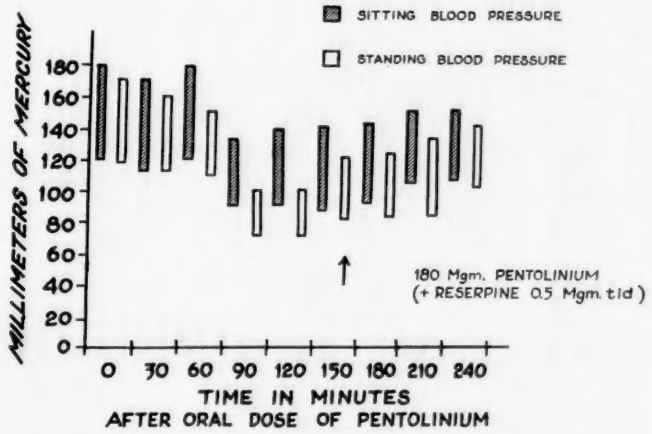

Fig. 1.—A graph representing the blood pressure response to an oral dose of pentolinium during one outpatient visit. The arrow denotes the pressure value which would be transferred to the graph drawn to illustrate the patient's long-term course as shown in Figs. 2-9. (Case 3, No. 296191.)

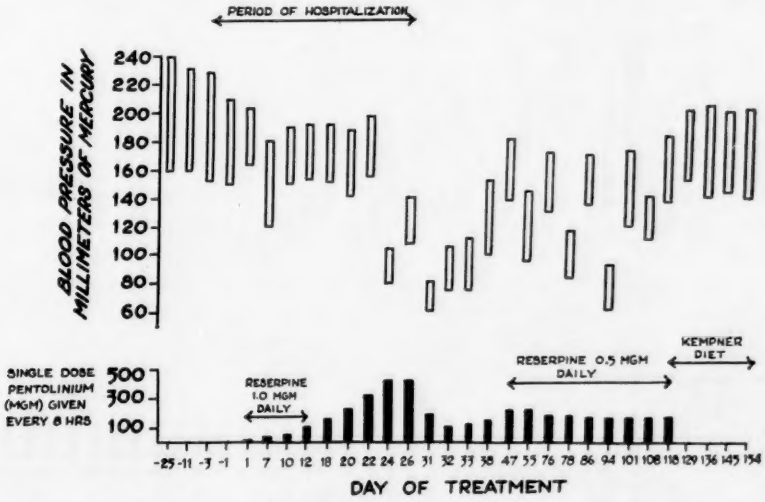

Fig. 2.—A graph representing the blood pressure response in Case 1 (No. 326294).

METHOD OF RECORDING RESULTS

An example of a series of arterial pressure determinations recorded in the course of one clinic visit during which a good response was observed is shown in Fig. 1. The third lowest reading with the patient standing (note arrow in Fig. 1) was selected as the value to be recorded to reflect the degree of blood pressure control achieved during the course of outpatient care. These readings are presented chronologically for each case in Figs. 2 to 9. This method of recording was chosen because it insured that pressure values equal to or below the

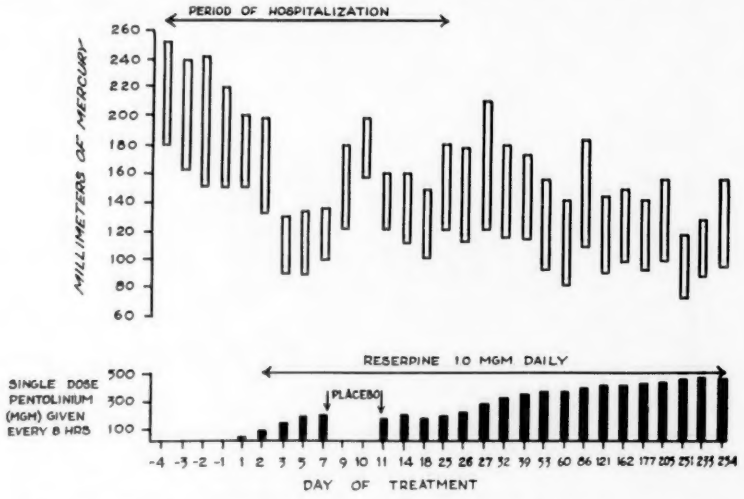

Fig. 3.—A graph representing the blood pressure response in Case 2 (No. 340062).

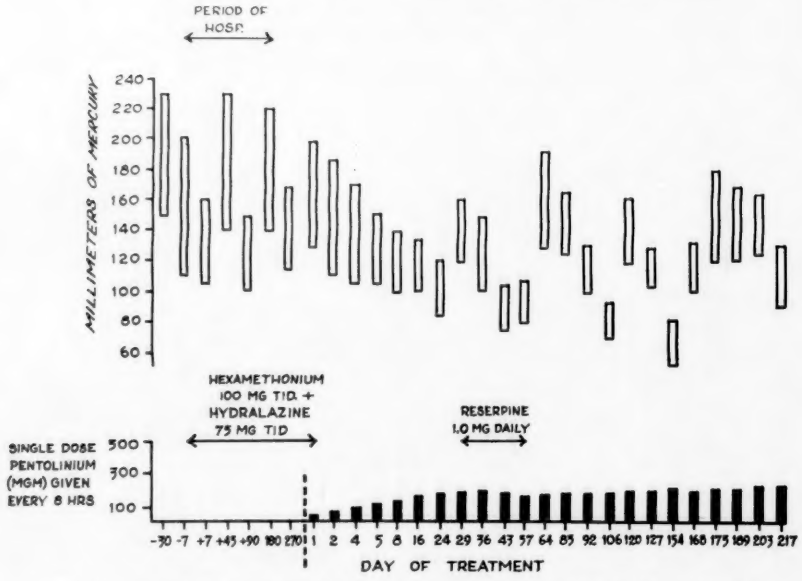

Fig. 4.—A graph representing the blood pressure response in Case 3 (No. 296191).

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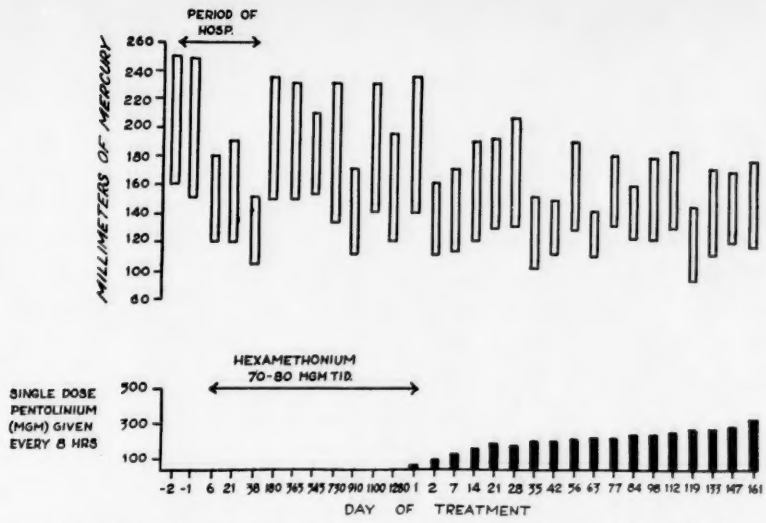

Fig. 5.—A graph representing the blood pressure response in Case 4 (No. 307598).

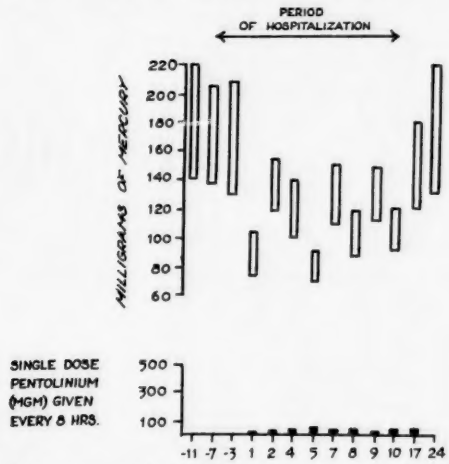

Fig. 6.—A graph representing the blood pressure response in Case 5 (No. 341031).

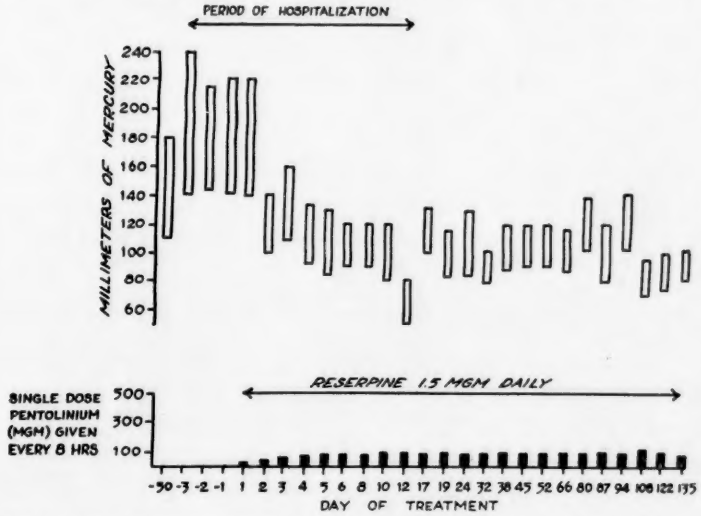

Fig. 7.—A graph representing the blood pressure response in Case 6 (No. 342705).

ones illustrated were achieved for at least one to two hours during each clinic visit. By this means, one avoids the error of placing too much weight upon very transient reductions in pressure which commonly occur. "Average blood pressure" would mean little since this would depend partly upon the length of the observation period.

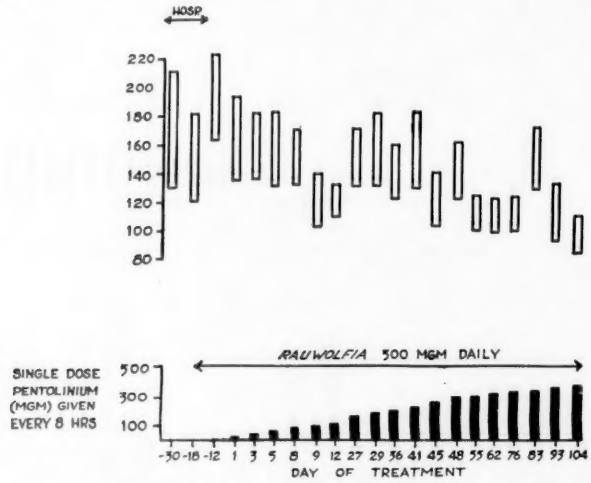

Fig. 8.—A graph representing the blood pressure response in Case 7 (No. 343334).

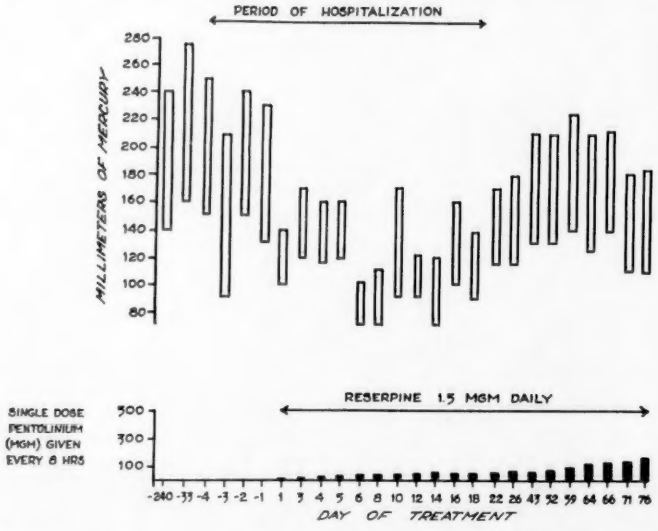

Fig. 9.—A graph representing the blood pressure response in Case 8 (No. 338255).

The blood pressure values presented in Figs. 2-9 as being taken before hospitalization or during hexamethonium treatment represent casual ones, and hence are not comparable to those shown as being obtained during the outpatient pentolinium treatment. The values representing determinations taken while the patients were in the hospital but before treatment are the lowest reading noted

during bed rest. Readings taken during pentolinium treatment in the hospital were recorded in a manner similar to that described for the illustration of the results of outpatient pentolinium treatment.

The criterion for the diastolic level was the disappearance of the sound. It was noteworthy that the Korotkow sounds became faint at the height of the drug effect in some of the patients in whom the usual transition from sharp to muffled sounds at the diastolic level was therefore difficult or impossible to identify.

RESULTS

The results observed may be described most clearly by the following case reports. The emphasis in the reports is upon the changes in symptoms, signs, and laboratory data pertinent to the hypertension. All the patients experienced uncomfortable effects from the drugs to some degree and these are discussed after the case reports.

CASE 1.—A 28-year-old Negro technician entered Stanford University Hospitals on Oct. 5, 1954, after he had been rejected as a blood donor because of high blood pressure first recognized in 1951. During the year prior to entry he had noted increasing fatigue. Frequent frontal headaches had been present for two weeks.

He was a heavy young man with an initial arterial pressure of 230/152 mm. Hg. Arteriolar narrowing, arteriovenous compression, and two large hemorrhages were noted in the retinae. The heart was slightly enlarged. There was an early diastolic gallop without other signs of heart failure.

There was minor proteinuria but no other urinary abnormality. The serum creatinine was 1.4 mg. per 100 c.c. An electrocardiogram showed the left ventricular hypertrophy pattern. Minimal left ventricular hypertrophy was suspected at radiologic examination.

Reserpine and pentolinium therapy was begun on the sixth hospital day. The reserpine was discontinued after two weeks because of nightmares; it was reinstituted on the forty-seventh day of treatment. Despite the development of a dry mouth, blurring of vision, constipation, and subjective feelings of faintness, no satisfactory blood pressure response occurred until the twenty-fourth day of treatment when a dose of 440 mg. thrice daily had been reached, as may be noted in Fig. 2. The day following his discharge on this dose, he returned to the hospital complaining of faintness. His pressure was found to be 82/60 mm. Hg and the dose was cut to 220 mg. Too great a hypotensive effect was noted on his first return visit to the outpatient clinic, and even further reductions were necessary to the order of 180 to 220 mg. every 8 hours. On this schedule there was often little or no response, but once or twice a week severe hypotensive symptoms would necessitate his leaving work. Because regulation seemed impossible, pentolinium was stopped and a Kempner diet and Rauwolfia 300 mg. a day were instituted. The patient was unable to follow the diet well and he eventually left the clinic.

During his period in the outpatient department, the retinal hemorrhages which had cleared in the hospital did not recur. There was no definite change in his cardiac status or in the results of laboratory examinations.

Comment.—This patient had experienced few symptoms prior to treatment and actually felt worse during therapy. The lability of his response seemed a reflection of his emotional lability. Thus when he was extremely agitated at being confined to the hospital the dose of pentolinium necessary to effect an arterial pressure response was twice that necessary in the outpatient department.

CASE 2.—A 37-year-old white truck driver entered Stanford University Hospitals on Oct. 25, 1954, complaining of shortness of breath for two weeks. He had a history of rheumatic fever at the age of 14, after which a murmur had been heard. In the summer of 1954, he had noted sudden onset of blurred vision in one eye. For one month he had noted shortness of breath,

swelling of the ankles, and frequent occipital headaches. At entry he was incapable of walking more than one level block.

He was a large, heavy man with massive ankle edema and an arterial pressure of 252/180 mm. Hg. Bilateral papilledema, retinal exudates, and hemorrhages were present. His neck veins were distended and the heart was enlarged to the anterior axillary line. An early diastolic gallop was present. Coarse râles were heard at the left lung base.

A moderate proteinuria was present. His serum creatinine was 1.6 mg. per 100 ml. The pattern of left ventricular hypertrophy was evident on the electrocardiogram and a chest film showed a generally enlarged heart.

On bed rest and a 3 Gm. salt diet the patient lost 25 poinds during a four-day period of diuresis and, as illustrated in Fig. 3, his arterial pressure declined to 220/150 mm. Hg. On the fifth hospital day pentolinium 20 mg. thrice daily and reserpine 0.5 mg. twice daily were begun. A satisfactory response was obtained by the third day of treatment. A two-day period of placebo treatment was followed by a rise in pressure. On the fourteenth day of treatment he was dismissed to the outpatient clinic with the symptoms of heart failure much improved and the papilledema resolved. However, during his first month of outpatient care, ankle edema persisted and two fresh retinal hemorrhages were noted. Early in the second month of outpatient care he had a three-day period of constipation followed by diarrhea which led to profound prostration, associated with orthostatic syncope, polyuria, and a loss of 20 pounds. Recovery took place with temporary cessation of pentolinium. Even after 36 hours without the drug his pressure was only 110/80 mm. Hg. Following that occurrence, all signs of heart failure disappeared and have not returned up to the ninth month of treatment. There has been no recurrence of retinal hemorrhage. A chest film has shown marked decrease in cardiac size. There has been no significant change in the serum creatinine, the urinalysis, or the electrocardiogram.

Comment.—This man, who had been in severe heart failure, returned to his work during the first month of treatment. He has had no symptoms of failure although his occupation requires considerable lifting as well as driving a truck within a lumber yard. His only treatment has been the antihypertension regimen plus the instruction to add no salt to his usual diet. Digitalis was withheld deliberately.

CASE 3.—A 34-year-old Negro construction worker entered San Francisco Veterans Hospital on Feb. 3, 1954, because of intermittent headaches for several months. In 1950 a low salt diet had been prescribed for asymptomatic high blood pressure. The patient had quit work two months before entry because of increasing shortness of breath, tiredness, and the severe headaches.

He was a young man of medium build with a blood pressure averaging 220/140 mm. Hg. His fundi showed many old and new hemorrhages and a slight degree of papilledema bilaterally. The apex impulse was at the anterior axillary line. The liver was 3 cm. below the costal margin and his ankles were swollen. A urinalysis revealed heavy proteinuria. His serum creatinine was 2.2 mg. per 100 ml. The pattern of left ventricular hypertrophy was evident on the electrocardiogram and a moderately enlarged heart was noted by x-ray.

After two entries he was finally dismissed on hexamethonium* 100 mg. thrice daily subcutaneously and hydralazine 75 mg. thrice daily, orally. He had had an appreciable reduction in pressure and the retinal hemorrhages and severe headaches had cleared. The signs of heart failure gradually improved. As shown in Fig. 4, his drug dosage was unchanged until pentolinium alone was substituted on Dec. 6, 1954. Except for the addition of reserpine from the twenty-ninth to fifty-seventh treatment days pentolinium has been the only drug prescribed.

Comment.—This patient's initial improvement took place on hydralazine and subcutaneous hexamethonium therapy. During the seven-month period on pentolinium alone, he has maintained that improvement. He prefers this oral medication and has no nocturia, which had been bothersome on hexamethonium. He has been doing light work as a commercial art student.

*Hexamethonium chloride was kindly supplied as Bistrium chloride by E. R. Squibb & Sons.

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CASE 4.—In April, 1951, this 26-year-old white housewife entered Stanford University Hospitals for consideration of sympathectomy. Her arterial pressure was said to have been high in 1948. For the three years prior to entry she had noted increasing fatigue. For one year she had had occasional shortness of breath and substernal pain on walking uphill. A premature placental separation interrupted an otherwise normal pregnancy in 1950.

She was a slim young woman whose initial pressure was 250/160 mm. Hg. Her fundi showed arteriolar narrowing, several small hemorrhages, and one exudate. There were no signs of heart failure.

There was a moderate proteinuria. The electrocardiogram was normal. Radiologic examination showed a normal-sized heart shadow with marked uncoiling of the aorta.

On the fifth hospital day hexamethonium chloride by subcutaneous injection was begun and the dose rapidly increased to 80 mg. three times a day, as noted in Fig. 5. By the end of the first month of treatment the retinal hemorrhages and exudate had cleared and have not returned. The slight exertional dyspnea and chest pain also cleared. About the ninth month of treatment she had a normal 4 pound child by cesarean section, done because of rapidly increasing proteinuria. After a short period without hexamethonium, this drug was again begun and soon increased to the same dosage. A short trial of oral hexamethonium did not seem effective and two 50 mg. doses of hydralazine resulted in violent headache, nausea, and vomiting. Pentolinium treatment was started in December, 1954, and after six months of treatment there has been no change in her physical findings. There is mild proteinuria but no nitrogen retention. The electrocardiogram remains within normal limits although left axis deviation has appeared. The chest film shows a slight cardiac enlargement and the same prominence of the aorta.

Comment.—This patient's blood pressure has never been under very good control as measured casually during administration of hexamethonium or more carefully while receiving pentolinium. Despite this she has done well over a four-year period as judged by the lack of harmful manifestations of hypertension. It may be that she would have done as well without drug therapy. She has had few undersirable effects from either hexamethonium or pentolinium, but has preferred the latter because it has been administered by mouth.

CASE 5.—A 39-year-old white housewife entered Stanford University Hospitals on Jan. 25, 1955, complaining of increasingly severe occipital headaches for the previous eight months. In 1949 she had had a thyroidectomy for hyperthyroidism. In 1949 and 1950, pregnancies had been accompanied by a rising arterial pressure. One pregnancy ended in a therapeutic abortion while the other terminated in a spontaneous abortion accompanied by convulsions. For several months she had noted exertional dyspnea and her physician had prescribed 1 mg. of reserpine and 200 mg. of hydralazine each day without achieving control of her high blood pressure. One week before entry she had a transient episode of numbness about her mouth and difficulty in speaking.

She was a well-nourished, middle-aged woman with bilateral proptosis. Retinal hemorrhages and exudates were present. The apex impulse was 2 cm. outside the midclavicular line, but no signs of congestive failure were present.

A mild proteinuria and a normal serum creatinine concentration were reported. The electrocardiogram and the chest film indicated left ventricular enlargement. Thyroid function tests were normal.

Because of the patient's emotional lability and tendency to feel depressed, pentolinium was started with reluctance. As illustrated in Fig. 6, a quite adequate pressure response was obtained in the hospital on 30 to 40 mg. thrice daily. However, her first outpatient trial showed no response to the drug. The day following this trial, she experienced a cerebrovascular accident of slow onset which resulted in a dysarthria and a right facial weakness. Her pressure was high four hours after a dose of pentolinium on the following day, and a trial dose of 50 mg. on the twenty-fourth day of treatment gave no response. The patient had another slight stroke a week after treatment was discontinued. Following three months' treatment with reserpine, her condition remains unchanged although a few fresh hemorrhages have appeared in her eye grounds.

Comment.—Unless the patient's enthusiastic cooperation is gained, treatment will fail. In this case, the patient was discouraged and was never certain that treatment was worth while. In addition there is no good evidence that treatment with the ganglion blocking agents is of any use in the avoidance of cerebrovascular accidents. Smirk[3] has advised a delay of six weeks before beginning treatment after a cerebrovascular accident.

CASE 6.—A 19-year-old white married stenographer entered Stanford University Hospitals on Feb. 15, 1955, with the complaint of seeing "spots before her eyes" for three weeks.

A year and a half previously, a pregnancy had been interrupted at five months because of ankle swelling, high blood pressure, and proteinuria. Following this episode she had got along well and her blood pressure dropped to "around 150." However, in October, 1954, she noted intermittent swelling of the ankles, and her physician said that the blood pressure and proteinuria were rising. When seen in late November as an outpatient by Dr. J. A. Leutscher, Jr., she had pitting edema of the ankles and a blood pressure of 180/110 mm. Hg. Her optic fundi were normal except for arteriolar narrowing. Her laboratory studies had shown the following values: Addis count of urinary sediment: 200 million erythrocytes, 10 million leukocytes, occasional oval fat bodies and granular casts, and 13 Gm. protein per 24 hours. The serum creatinine concentration was 1.3 mg. per 100 ml., that of cholesterol was 600 mg. per 100 ml., and the concentration of albumin and globulin were 1.9 and 2.1 Gm. per 100 c.c. serum, respectively.

Following this visit her ankle swelling had continued. During the three weeks prior to entry she had noted increased blurring of vision accompanied by the seeing of spots before her eyes. She had noted parietal headaches during the three weeks.

She was a well-nourished young woman with a slightly puffy face. There was moderate periorbital and minimal ankle edema. Visual acuity was 8/200 in each eye. The only other abnormal findings were limited to the optic fundi, in both of which there were extensive exudates, hemorrhages, and papilledema of one to two diopters. Laboratory studies were nearly the same as those of November. Neither the chest film nor electrocardiogram revealed any abnormality.

Reserpine 0.5 mg. thrice daily and pentolinium were begun on her fourth hospital day; by the second day of treatment a satisfactory response was achieved and maintained by raising the dose of pentolinium to 90 to 110 mg. thrice daily (Fig. 7). After fourteen days of treatment she was dismissed, having lost 9 pounds during her stay. No edema was detectable and papilledema had vanished. In the outpatient clinic the same dose of pentolinium and reserpine was found to result in a blood pressure close to or within normal limits during every four-hour testing period. After four months of treatment there has been marked clearing of the eye grounds and her visual acuity has improved to 20/25 bilaterally. The only fresh hemorrhage to appear after treatment was begun occurred on the third day of treatment. No edema has been noted during her outpatient course. The serum creatinine concentration is 1.8 mg. per 100 ml. and that of cholesterol is 442 mg. per 100 ml. The urinary findings, chest film, and electrocardiogram are unchanged. She has resumed work, and with the exception of needing glasses for close work she has had almost no undesirable effects from the drugs.

Comment.—It is most probable that this patient's hypertension was secondary to renal disease as evidenced by the nephrotic syndrome. The prompt lowering of her pressure during therapy coincided with the clearing of the signs of retinal damage. It may be that the process initiating the severe hypertension has now subsided and that the patient can get along without treatment. This would seem unlikely, however, since the urinary and serum findings of nephrosis persist.

CASE 7.—A 43-year-old Negro scavenger entered San Franciso Hospital on Feb. 20, 1955, complaining of palpitation and shortness of breath for several months.

During examination in 1951 his blood pressure had varied from 130/90 to 140/110 mm. Hg, and his electrocardiogram had shown the pattern of the Wolff-Parkinson-White syndrome. He

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noted no symptoms until the fall of 1954, when increasing shortness of breath occurred after exercise and at night. His immediate reason for entry was related to supraventricular tachycardia which had lasted for a day and which had been present intermittently for the previous month. His fundi were reported to show hemorrhages.

There was a moderate proteinuria and the serum creatinine concentration was 2.9 mg. per 100 ml. The electrocardiograms showed paroxysmal supraventricular tachycardia associated with the Wolff-Parkinson-White syndrome.

On bed rest, a low salt diet, quinidine, and Rauwolfia 500 mg. daily, his blood pressure varied from 210/130 to 180/120 mm. Hg, his tachycardia ceased and his symptoms improved. He was discharged on Rauwolfia alone and instructed to add no salt to his diet.

He was seen in the Stanford Outpatient Department on March 21, 1955. He complained of having had mild shortness of breath and a very rare bout of palpitation after leaving the hospital. His ankles had begun to swell despite moderate salt restriction and limited activity. Retinal arteriolar narrowing and arteriovenous compression were present. The apex impulse was just within the anterior axillary line. A gallop rhythm and systolic murmur were heard. His liver was 5 cm. below the costal margin and there was slight ankle edema. His standing blood pressure was 190/140 mm. Hg. The laboratory data were unchanged.

Pentolinium was begun on March 28, continuing the 500 mg. of Rauwolfia and mild salt restriction. After 40 days of treatment there had been no consistent response to the treatment (Fig. 8). Two fresh retinal hemorrhages had appeared. His liver edge was still 5 cm. below the costal margin and he had more marked ankle edema. Thereafter, better response to the drug was noted and three weeks later the liver was no longer palpable and the ankle edema was minimal. After three and one-half months of treatment the signs of congestive failure have disappeared although there has been no change in heart size clinically. No new retinal hemorrhages have appeared.

Comment.—Although this patient had symptoms of heart failure while on restricted activity and a high dose of Rauwolfia he has been able to do the fairly heavy labor of a presser in a laundry while on treatment with pentolinium. Feelings of faintness while at work have been more bothersome than any symptom of heart failure.

CASE 8.—A 45-year-old Negro male cook entered Stanford University Hospitals, April 13, 1955. He complained of shortness of breath for two weeks.

He had been seen in the outpatient clinic in August, 1954, because of high blood pressure, then 240/140 mm. Hg. He had no symptoms. Fundi showed some arteriolar narrowing. He had a marked proteinuria and his serum creatinine was measured at 1.7 mg. per 100 ml. The chest film showed left ventricular enlargement. Despite a weight reduction of 13 pounds and intermittent treatment with Rauwolfia, the patient noted increasing shortness of breath and ankle swelling in late March, 1955. On the day of entry he was able to walk only a half block or climb three steps, and had to sit up at night.

He was a moderately obese man, who was short of breath while sitting up. He had numerous, small flame-shaped retinal hemorrhages. The neck veins were distended. The apex impulse was at the anterior axillary line and there was a moderate systolic murmur along the left sternal border and at the apex. Râles were heard up to the midscapular area over both lung fields posteriorly. The liver was 3 cm. below the costal margin and there was moderate pitting edema of the ankles and sacral region.

Nitrogen retention was evidenced by a serum creatinine concentration of 2.7 mg. per 100 ml., and urinalysis showed a marked proteinuria. A pattern of left ventricular hypertrophy was present in the electrocardiogram. The chest film showed a generally enlarged heart shadow.

The patient was put on bed rest, digitalized, and given one injection of a diuretic. After one week, he had lost 17 pounds and was feeling much more comfortable. On the fifth hospital day pentolinium was started (as a small 2.5 mg. dose because of nitrogen retention) and it was gradually increased to 40 mg. thrice daily in addition to reserpine 0.5 mg. thrice daily. As shown n Fig. 9, this dosage seemed to result in adequate blood pressure control in the hospital, but it

was not nearly enough for outpatient care. After six weeks of outpatient treatment, there was little demonstrable hypotensive effect. Fresh retinal hemorrhages and basal râles were noted. After two and one-half months of treatment, the blood pressure response is still inadequate to a dose of 175 mg., but the retinal hemorrhages have cleared and the râles are only occasionally present. He has had occasional feelings of faintness, but has been able to work eight hours a night as a cook.

Comment.—This is the only patient of the series taking supplementary digitalis. It is likely that the digitalis and a 3 gm. salt diet have been more important in alleviating his symptoms of heart failure than the antihypertensive regimen, which after two and one-half months has not demonstrably lowered his pressure during outpatient care.

DISCUSSION

These results of the use of pentolinium in a small group of patients with severe hypertension agree with reports of more extensive experience in the use of ganglion blocking agents.[2-5] Papilledema, retinal hemorrhages, and the signs and symptoms of heart failure have cleared following the institution of adequate control of the blood pressure with pentolinium and reserpine. Although there was no significant change in the electrocardiographic pattern in this group of patients, improvement has been noted by others.[3,4] In this series, the signs of renal damage remained about the same during the period of treatment.

Actually, the clearing of the objective signs of damage complicating the hypertension was more striking than the degree of blood pressure control attained. The variability of response is amply demonstrated in Figs. 2 to 9. The patients' pressures were at or under those recorded in the charts for only one to two hours during the ideal trial conditions. If the other doses throughout the day resulted in similar reductions, then pressures in the range presented in the charts would be achieved for only about six hours a day. Evidently this amount of relief from the higher levels is enough to protect the patients against many of the damaging effects.

Undersirable effects other than severe hypotensive episodes were bothersome to the patients but did not result in the stopping of treatment in any case. In those patients whose occupations required close vision, loss of accommodation was troublesome, but was most satisfactorily corrected by the use of positive lenses. Constipation was usually well controlled by the use of milk of magnesia. Loss of potency occurred in every male patient. The patients accustomed themselves well to the dry mouth, feelings of chilliness, and the sitting posture during the night. No urinary symptoms were noted.

The unpredictability of response caused treatment to be stopped in Case 1, and a cerebrovascular accident probably unrelated to treatment discouraged further pentolinium administration in Case 5.

This type of control requires a great deal of effort and patience from the patient and is time-consuming to the doctor unless he can delegate much of the blood pressure reading to an assistant. But any less observation of the patient than outlined here would lead to less accurate control of the pressure. Despite our evaluation of the four-hour trial response to the drug before increasing the do-

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sage, most of the patients in this series had severe hypotensive reactions at one time or another.

The recommendation of some observers that patients should determine their own pressures at home was not followed, because of concern over the psychologic aspects of this procedure as well as the question of accuracy of such observations.

This seems a method of treatment well worth while in selected severe hypertensive patients, but probably not in the less severe hypertensive at this time. Meanwhile, a better drug with more uniform and prolonged action and fewer undesirable effects is awaited.

SUMMARY

Eight cases of severe hypertension treated with pentolinium are presented. Treatment was discontinued in one patient because of the unpredictability of hypotensive response. A cerebrovascular accident discouraged treatment in the other case. Unpleasant drug effects other than the hypotensive one caused no discontinuance of treatment although all patients experienced such effects to a variable degree.

Six are continuing treatment. Among these all showed clearing of retinal hemorrhages. Papilledema cleared in the three cases in which it had been present. Three of four patients showed disappearance of the signs of heart failure while on antihypertension drugs alone, and the fourth showed improvement but this may have been primarily due to digitails. The renal status and electrocardiographic pattern stayed essentially constant in all patients.

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ANTERIOR AND POSTERIOR WALL INFARCTION OF THE HEART: A STATISTICAL COMPARISON BASED ON AUTOPSY FINDINGS

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(Received for publication Dec. 2, 1955.)

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THE two most usual sites of myocardial infarction are in the anterior wall of the left ventricle near its apex and in its posterior wall close to the base. It has been our casual observation at necropsy that posterior wall infarcts tend, as a rule, to be smaller and to involve the adjacent endocardium less extensively than anterior wall lesions. As a consequence, mural thrombi are less frequently found on the posterior surface of the left ventricle than at the apex or on the anterior wall. Reference to numerous statistical surveys and recent texts indicates that such differences have not been clearly recognized. In fact, in the recent monograph of Wright and his collaborators,[1] in which the statistics of many observers are compiled, it is stated that thromboembolic phenomena are encountered clinically with equal frequency in both types of infarction. This suggests that our impressions at routine necropsy might not be supported by a detailed analysis of a large series of cases or that the left ventricle is not the major source of emboli in myocardial infarction.

It is now possible in most cases to distinguish electrocardiographically with fair accuracy between anterior and posterior wall myocardial infarction. It seems surprising, therefore, that a systematic comparison of the chief pathologic features of each type has not been made. Distinctive differences, if they exist, might have clinical significance.

TABLE I. LOCATION OF MYOCARDIAL INFARCTS

SITE OF INFARCT	NO.	%
Anterior wall	297	41.2
Posterior wall	217	30.1
Anterior and posterior walls	97	13.5
Interventricular septum only	60	8.3
Left ventricle, diffuse, multiple or site not specified	30	4.2
Atypical, right ventricle only or chamber not specified	20	2.8

This investigation was supported by Research Grant #H-1088(C) from the National Heart Institute of the National Institutes of Health, Public Health Service.

The present study is based on a consecutive series of 721 cases of myocardial infarction examined at necropsy from 1944 to 1954 at Bellevue Hospital. Areas of muscle necrosis or of scarring of more than 1 cm. in diameter in two dimensions were classified as infarcts. The location of the infarcts is listed in Table 1. Included among the anterior and posterior wall groups are many large infarcts that involved the interventricular septum, lateral walls, apex or right ventricle by direct extension from the original focus. In 514 (71.3 per cent) of the 721 hearts the single infarct was located primarily in the anterior apical or posterior basal region of the left ventricle.

In 97 (13.5 per cent) other hearts both regions were involved by independent infarcts. Both infarcts were recent in 16; both recent and healed in 18; both completely healed in 27. Of the remainder, 19 had recent anterior and healed posterior lesions; 17 had recent posterior and healed anterior ones. These observations suggest that the site of an initial infarct has little bearing on the frequency with which a second infarct will develop on the opposing wall of the ventricle.

The remainder of the analysis will be based on the 514 cases in which infarcts were limited to a single wall of the heart.

Incidence.—Table II shows the incidence of (1) recent, (2) recent and healed, and (3) healed infarcts. Included in the recent and healed group are those cases in which there was evidence of superimposed recent infarction in and around areas of old infarctions. Anterior wall infarcts are more numerous than posterior wall ones in the ratio of 1.37:1. An equal percentage (57.0 and 56.2) of both groups survive to complete healing. Approximately one-fourth of each group dies during the initial attack. Acute posterior wall infarction appears to be slightly more fatal than acute anterior wall infarction. On the other hand, persons with anterior wall infarctions seem to be slightly more vulnerable to new superimposed infarcts in the same region. Neither of these differences are, however, great enough to be statistically significant.

TABLE II. INCIDENCE AND TYPE OF ANTERIOR AND POSTERIOR WALL INFARCTS

SITE AND TYPE OF INFARCT	NO.	% OF TOTAL ANTERIOR OR POSTERIOR	RATIO ANTERIOR:POSTERIOR
Recent anterior	66	22.2	
Recent posterior	57	26.7	1.16:1
Recent and healed anterior	62	20.9	
Recent and healed posterior	38	17.5	1.63:1
Healed anterior	169	57.0	
Healed posterior	122	56.2	1.39:1
Total anterior	297		
Total posterior	217		1.37:1

Age and Sex.—The age and sex distributions of anterior and posterior wall infarcts are very similar (Table III). About 3 times as many men as women had infarcts in each location. The sex difference in incidence is most marked in the

younger age groups. The incidence of infarction in women under 50 years of age is too low for statistical comparison. However, when the figures of both sexes are combined, it is found that before the age of 65 years posterior wall infarcts are only slightly less numerous than anterior wall ones. After 65, anterior wall infarcts predominate in a ratio of over 1.5:1.

TABLE III. AGE AND SEX DISTRIBUTION OF ANTERIOR AND POSTERIOR WALL INFARCTS

SITE OF INFARCT	34–49 YR.		50–64 YR.		65–79 YR.		80 YR. & OVER		TOTAL	
	MEN	WOMEN	MEN	WOMEN	MEN	WOMEN	MEN	WOMEN	MEN	WOMEN
Total anterior wall	21	3	79	23	103	39	19	10	222	75
Total posterior wall	13	5	69	20	69	26	10	5	161	56
Ratio of men:women										
Anterior wall	7.0:1		3.4:1		2.6:1		1.9:1		3.0:1	
Posterior wall	2.6:1		3.5:1		2.6:1		2.0:1		2.9:1	

Size of Infarcts.—The size of the infarcts was not recorded in adequate detail in 61 cases. Among the remaining 453, infarcts that were more than 3 cm. in diameter in one dimension were classified as large. In Table IV it may be seen that a higher percentage of recent than of healed infarcts in both groups are large. This might be expected, as large infarcts undoubtedly lead to early death and all infarcts shrink in size on healing. More inexplicable is the finding that anterior wall infarcts in men tend to be larger in size than posterior wall ones and that the

TABLE IV. COMPARATIVE SIZE OF ANTERIOR AND POSTERIOR WALL INFARCTS

SITE AND TYPE OF INFARCT	MEN			WOMEN			TOTAL		
	LARGE	SMALL	% LARGE	LARGE	SMALL	% LARGE	LARGE	SMALL	% LARGE
Recent anterior	31	9	77.5	10	9	52.6	41	18	69.5
Recent posterior	24	13	64.9	13	5	72.2	37	18	67.3
Recent and healed anterior	32	7	82.1	8	6	57.1	40	13	75.5
Recent and healed posterior	20	5	80.0	3	6	33.3	23	11	67.6
Healed anterior	50	56	47.2	14	21	40.0	64	77	45.4
Healed posterior	31	53	36.9	13	10	56.5	44	63	41.1
Total anterior	113	72	61.1	32	36	47.1	145	108	57.3
Total posterior	75	81	48.1	29	21	58.0	104	102	50.5

opposite is the case in women. This appears to be true for both recent and healed esions. No adequate explanation can be offered other than the suggestion that the anterior descending branch of the left coronary artery, in particular, is more extensively involved by atherosclerosis in men than in women.

Accuracy of Clinical Diagnosis.—Thirty per cent of each type of infarct was correctly diagnosed as such (without regard to localization) during life

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(Table V). Recent infarcts of both types were more often clinically manifest than healed ones. There is some suggestion that healed posterior wall infarctions in women are more often recognized than healed anterior wall ones. This is further borne out if accuracy of clinical diagnosis of large infarcts only is

TABLE V. ACCURACY OF CLINICAL DIAGNOSIS OF ANTERIOR AND POSTERIOR WALL INFARCTS

	MEN			WOMEN			TOTAL		
	DETECTED CLINICALLY		PER CENT DETECTED	DETECTED CLINICALLY		PER CENT DETECTED	DETECTED CLINICALLY		PER CENT DETECTED
	YES	NO		YES	NO		YES	NO	
Recent anterior	25	20	55.6	7	14	33.3	32	34	48.5
Recent posterior	17	21	44.7	7	12	36.8	24	33	42.1
Recent and healed anterior	19	28	40.4	5	10	33.3	24	38	38.7
Recent and healed posterior	13	14	48.2	5	6	45.3	18	20	47.4
Healed anterior	22	108	16.9	8	31	20.5	30	139	17.8
Healed posterior	17	79	17.7	8	22	37.5	25	101	19.8
Total anterior	66	156	29.7	20	55	26.7	86	211	29.0
Total posterior	47	114	29.2	20	40	33.3	67	154	30.3

TABLE VI. ACCURACY OF CLINICAL DIAGNOSIS OF LARGE ANTERIOR AND POSTERIOR WALL INFARCTS

	MEN			WOMEN			TOTAL		
	DETECTED CLINICALLY		PER CENT DETECTED	DETECTED CLINICALLY		PER CENT DETECTED	DETECTED CLINICALLY		PER CENT DETECTED
	YES	NO		YES	NO		YES	NO	
Recent anterior	15	16	48.4	5	5	50.0	20	21	48.8
Recent posterior	12	12	50.0	6	7	46.2	18	19	48.6
Recent and healed anterior	15	17	46.9	2	6	25.0	17	23	42.5
Recent and healed posterior	9	11	45.0	3	0	100.0	12	11	52.2
Healed anterior	9	41	18.0	2	12	14.3	11	53	17.2
Healed posterior	6	25	19.3	7	6	53.8	13	31	29.5
Total anterior	39	74	34.5	9	23	28.1	48	97	33.1
Total posterior	27	48	36.0	16	13	55.2	43	61	41.3

tabulated (Table VI). It is remarkable that, in general, large infarcts are not much more frequently detected clinically than small ones. No attempt was made correlate electrocardiographic localization of infarcts with the autopsy findings.

Incidence of Intracardiac Thrombi.—A striking difference between anterior and posterior wall infarcts is in the incidence of endocardial thrombi (Table VII) in all chambers of the heart. Thrombi in the left ventricle are more than twice as

TABLE VII. INCIDENCE OF INTRACARDIAC THROMBI IN ANTERIOR AND POSTERIOR WALL INFARCTION

SITE AND TYPE OF INFARCT	LOCATION OF THROMBI								WITHOUT ANY THROMBI	
	LEFT VENTRICLE		RIGHT VENTRICLE		LEFT AURICLE		RIGHT AURICLE		NO.	%
	NO.	%	NO.	%	NO.	%	NO.	%		
Recent anterior	32	48.5	5	7.6	5	7.6	5	7.6	29	43.9
Recent posterior	16	28.1	1	1.8	4	7.0	2	3.5	39	68.4
Recent and healed anterior	32	51.8	4	6.5	2	3.2	10	16.1	25	40.3
Recent and healed posterior	7	18.4	2	5.3	5	13.2	3	7.9	24	63.2
Healed anterior	43	25.4	6	3.6	11	6.5	18	10.7	112	66.3
Healed posterior	15	12.3	1	0.8	5	4.1	10	8.2	100	82.0
Total anterior	107	36.1	15	5.1	28	9.4	33	11.1	166	55.9
Total posterior	38	17.6	4	1.8	14	6.5	15	6.9	160	73.7

common in anterior wall infarction as in posterior wall infarction. This difference is greater than can be accounted for by differences in size of the two types of infarcts alone. The basal portion of the left ventricle is thicker than the apical regions and basal infarcts are frequently deeply situated and do not extend to the endocardium. In anterior apical infarction, the apical portion of the right ventricle is sometimes involved, leading to thrombus formation at this latter site. The right ventricle is seldom involved in posterior wall infarction. No explanation can be given for the difference in incidence of thrombi in the auricular appendages but this difference is not nearly as pronounced as in the ventricles. Reference to Table II discloses that the proportion of persons who die during the early stages of posterior wall infarction is slightly larger than the proportion of those who die during early anterior wall infarction. It may be argued from these observations that the development of intracardiac thrombosis as a complication of myocardial infarction is not a decisive and perhaps not even an important factor in causing death.

The majority of cases in this series received no anticoagulant therapy. Some of both the recent anterior and posterior groups received such treatment but in varying amounts and for varying periods of time. If these cases are excluded from our computations, the difference in incidence of intracardiac thrombosis in the two groups is essentially unchanged.

Pericarditis and Rupture.—A pronounced difference between recent anterior and posterior wall infarction is found in the incidence of acute pericarditis

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(Table VIII). One-third of the anterior lesions but only one-tenth of the posterior ones had this complication. Even among those who survive the initial lesion and have superimposed infarcts or heal completely, the incidence of pericardial involvement is greater in the groups with anterior wall infarcts. The reasons for this difference are probably the same as those that account for differences in

TABLE VIII. INCIDENCE OF PERICARDITIS AND MYOCARDIAL RUPTURE IN ANTERIOR AND POSTERIOR WALL INFARCTION

SITE AND TYPE OF INFARCT	ACUTE PERICARDITIS		HEALED PERICARDITIS		MYOCARDIAL RUPTURE	
	NO.	%	NO.	%	NO.	%
Recent anterior	22	33.3	2	3.0	4	6.1
Recent posterior	6	10.5	2	3.5	2	3.5
Recent and healed anterior	13	21.0	5	8.1	1	1.6
Recent and healed posterior	6	15.8	3	7.9	0	—
Healed anterior	8	4.7	22	13.0	0	—
Healed posterior	3	2.5	11	9.1	0	—

endocardial involvement, namely, that a higher percentage of posterior lesions are small and are located in a thicker portion of the myocardium than are anterior wall lesions. Consequently, posterior wall lesions involve the adjacent inner and outer surfaces of the heart less often and less extensively.

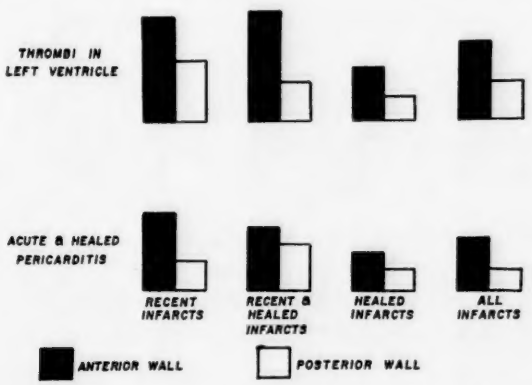

Fig. 1.—Comparison of the incidence of mural thrombi and pericardial lesions in anterior and posterior wall infarcts of the heart. The height of the vertical columns is based on the percentage of hearts involved in each category.

Only seven instances of external myocardial rupture are found in the entire series. These are too few to determine whether the location of infarcts plays a significant role in the development of this complication. However, it is known[2] that the majority of external ruptures occur in the anterior wall near the apex.

Hypertension and Cardiac Hypertrophy.—Clinical evidence of hypertension is obtained in 15.1 per cent of all persons over 35 years of age who are examined at necropsy in Bellevue Hospital. An equal proportion (about one-third) of cases of healed anterior and posterior infarcts had clinical evidence of hypertension (repeated blood pressure over 145/95 mm. Hg). In over one-half of each group the heart was hypertrophied (heart weight greater than 360 grams in women and 410 grams in men). No clinical evidence of hypertension was noted in 29 per cent of the cases of both categories with enlarged hearts. Since there is no other obvious cause for hypertrophy in most of these, it may be presumed that many may have been hypertensive prior to myocardial infarction. The incidence of hypertrophy is as great in acute as in healed infarction in both groups (Table IX). This finding does not support the belief that in some instances the healing of an infarct may lead to secondary hypertrophy.[3] The high incidence of hypertrophy in cases of acute infarction favors the view that hypertrophied hearts are more susceptible to this lesion than normal-sized ones. However, this association could be accidental since hypertension may promote the development of coronary artery atherosclerosis as well as cardiac hypertrophy.

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TABLE IX. INCIDENCE OF HYPERTENSION AND CARDIAC HYPERTROPHY IN ANTERIOR AND POSTERIOR WALL INFARCTION

SITE AND TYPE OF INFARCT	WITH HYPERTENSION		WITH CARDIAC HYPERTROPHY		HYPERTROPHY WITHOUT HYPERTENSION	
	NO.	%	NO.	%	NO.	%
Recent anterior	24	36.4	37	56.7	19	28.8
Recent posterior	28	49.1	35	61.4	13	23.2
Recent and healed anterior	25	40.3	44	71.0	22	35.5
Recent and healed posterior	15	39.5	20	52.6	11	28.9
Healed anterior	56	33.1	97	57.4	35	29.6
Healed posterior	40	32.8	63	51.6	35	28.7

The incidence of hypertension is considerably higher in the group with acute posterior wall than in that with acute anterior wall infarction. This suggests that in acute infarction that ends fatally, lesions situated anteriorly more often cause a drop in hypertensive blood pressure levels than do posterior wall lesions.

Diabetes and Obesity.—The incidence of diabetes in both groups is surprisingly low (11.1 per cent of the anterior wall and 13.4 per cent of the posterior wall group). In the Bellevue necropsy series 6.7 per cent of all persons over 35 years of age are diabetic. The incidence of diabetes is higher (22.8 per cent) in the group with acute posterior wall infarcts than in those with acute anterior wall lesions (12.1 per cent). According to Wright, Marple, and Beck,[1] diabetics with acute myocardial infarction have a poor survival record. Coincidental diabetes may thus be a factor in the relative high death rate found in acute posterior wall infarction. It could, in fact, neutralize any favorable effect the pau-

city of endocardial and pericardial involvement may afford in this group. Coincidental obesity is low in all groups (7.4 per cent) of the entire series and could not be related in any way to the location or age of the infarcts.

SUMMARY

Statistical analysis of 514 cases of anterior and posterior wall infarcts of the heart reveals that the chief pathologic features of both types are similar. Anterior apical infarcts often extend to the adjacent endocardium and epicardium, and thus give rise to mural thrombus formation and pericarditis more frequently than do posterior basal ones. The differences in incidence of these complications in the two types of infarcts are great enough to be reasonably conclusive ones.

Differences in incidence of other characteristics are also noted but these are not of sufficient magnitude to exclude the possibility of chance variation. Some of these unproved differences would be of clinical importance if they could be confirmed by other analyses. They will, therefore, be summarized briefly: (1) The ratio of anterior wall to posterior wall infarction may increase progressively with advancing age. (2) Acute posterior wall infarction may have a slightly higher mortality rate than acute anterior wall infarction despite the lower incidence of mural thrombosis and pericarditis in the former. (3) Superimposed new infarcts in areas of old infarction may be found more frequently in the anterior wall. (4) Anterior wall infarcts in men tend to be larger than posterior wall lesions; the reverse may be true in women. (5) Healed posterior wall infarcts in women may be more often clinically manifest than other healed infarcts. (6) Thrombi in the right ventricle and both auricular appendages, as well as in the left ventricle, may less frequently complicate posterior than anterior wall infarction. (7) Pre-existing hypertension may persist more frequently in acute posterior wall than in acute anterior wall infarction and may be a poor prognostic sign. (8) The coincidence of diabetes may be particularly high in fatal acute posterior wall infarction.

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STUDIES OF THE ARTERIAL PULSE WAVE

I. The Normal Pulse Wave and Its Modification in the Presence of Human Arteriosclerosis

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(Received for publication Dec. 3, 1955.)

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DESPITE intensive investigation[1-7] of the mechanism and mode of propagation of the arterial pulse wave, little or no attempt has been made to correlate changes in its configuration with disease states. This report is a study of the arterial pulse wave from the clinician's viewpoint, with particular reference to changes in the pulse wave contour in patients diagnosed clinically as having peripheral arteriosclerosis.

A major drawback to clinical studies has been the lack of proper instrumentation. Sphygmographs and oscillographs of various types have been in use for years, but their many disadvantages have slowed interest in this field. Observations with these instruments have been extensively reviewed by von Recklinghausen.[8] None has proved satisfactory, either for research purposes or for clinical use. They have a variety of defects in common. In general, sensitivity is so slight that adequate study of the component phases of the pulsation is difficult. Standardization of the pulse wave tracings has not been achieved, and therefore the results are not reproducible in the individual subject. Finally, the results obtained with these instruments do not correlate well with clinical estimation of the state of the peripheral circulation, since careful examination may reveal minute pulsations and adequate temperatures in parts where the pulse wave is recorded as absent. Indeed, Allen, Barker, and Hines[9] conclude that: "Oscillometry has been one of the least valuable of all methods of investigation of the peripheral circulation."

Stimulated by an interest in the study of the arterial pulse wave in arteriosclerosis, one of us (H.L.) has devised a highly sensitive instrument for studying the characteristics of the arterial pulse wave in health and disease. This instrument has tentatively been designated a "Vasculograph" and its recordings as "Vasculograms."

This investigation was supported in part by a research grant (H-1185) from the National Heart Institute of the National Institutes of Health, Public Health Service, and by grants from the New York Heart Association and the Albert and Mary Lasker Foundation.

Experiences with the Vasculograph over the past six years* indicate that arterial pulse wave tracings, as recorded by the instrument, may be useful in the study of human and experimentally induced arteriosclerosis. It is the intent of this paper to describe the technical aspects of the Vasculograph and to report on the changes in arterial pulse contour in normal subjects and in patients with clinical arteriosclerosis.

THE INSTRUMENT

The basic principle upon which the instrument operates is that of converting pressure waves into electrical energy. The electrical impulses are then amplified and recorded. A sensitive rubber cuff with an inelastic backing is applied to the external surface of the limb or digit to be tested. This cuff is connected by a system of tubing to a diaphragm mechanically linked to a piezo-electric crystal. By this means the crystal transforms pressure changes in the cuff, due to arterial pulsations, into changes in electrical potential. These changes in potential are amplified and actuate a string-type mirror galvanometer and are recorded on standard 12 cm. wide electrocardiograph paper. The pressure within the cuff can be elevated to any desired level. Arterial pulsations appear to be greatest when the applied pressure approximates the intra-arterial diastolic pressure. The applied compressing or cuff pressure is recorded simultaneously.†

Recordings are taken with the patient in a supine or sitting position. The inflatable cuff is applied over the digit or limb to be tested and the pressure within the cuff is slowly increased from zero to a point above the patient's systolic blood pressure. The pulse wave can be observed as an oscillating beam of light. The magnitude of the oscillations increase as the pressure within the inflatable cuff approaches the diastolic pressure within the vessel. The sensitivity control is adjusted so that, at its maximum, the amplitude of the pulse wave will be slightly less than the width of the recording paper. The pressure is let out of the inflatable cuff and then reapplied with the sensitivity already fixed. On this second rise of pressure, a recording of the moving light beam is made. Recordings can be made at either a constant pressure within the cuff or as the applied pressure is increased or decreased. Optimal amplitude of the recording is obtained when the applied pressure is approximately 10 mm. Hg below the patient's diastolic pressure level. The procedure is a simple one, and, as with the electrocardiograph, a complete set of tracings can be taken in fifteen to twenty minutes.

Results are reproducible in the same subject over varying conditions of time, season of the year, position of the patient, previous activity, and room temperature and humidity. Few precautions are necessary in taking recordings. Smoking cigarettes just prior to a recording or a very cold digit reduces the over-all amplitude but does not affect the configuration of the pulse wave.

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*These studies were started by the senior author in 1936 in Hungary and continued at the Maimonides Hospital of Brooklyn from 1949 to 1951.

†A description of the technical details of the instrument is presented in the Appendix.

THE NORMAL VASCULOGRAM

Fig. 1 is a reproduction of a Vasculogram recorded from the finger of a 25-year-old healthy man with the applied pressure within the inflatable cuff at 48 mm. Hg. The component parts of the normal arterial pulse wave may be studied from this tracing. There is an initial wave and a well-defined dicrotic wave.

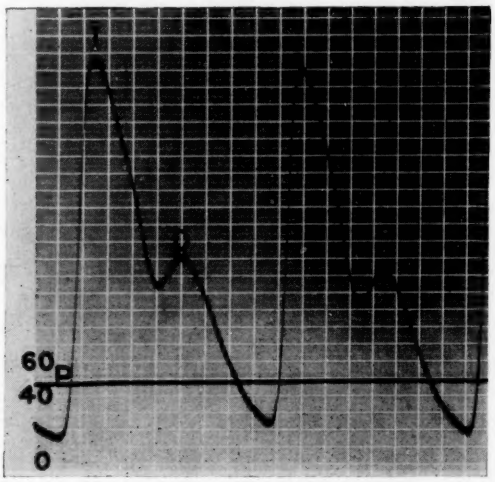

Fig. 1.—Normal arterial pulse waves recorded from the third digit of a healthy 25-year-old man. The vertical lines are time signals 0.1 second apart and the horizontal lines represent pressure increments of 10 mm. Hg. in the cuff applied about the finger. The cuff pressure (P) is recorded simultaneously but independently of the components of the pulse wave form. Note the initial wave (*I*) and the well-defined dicrotic wave (*D*).

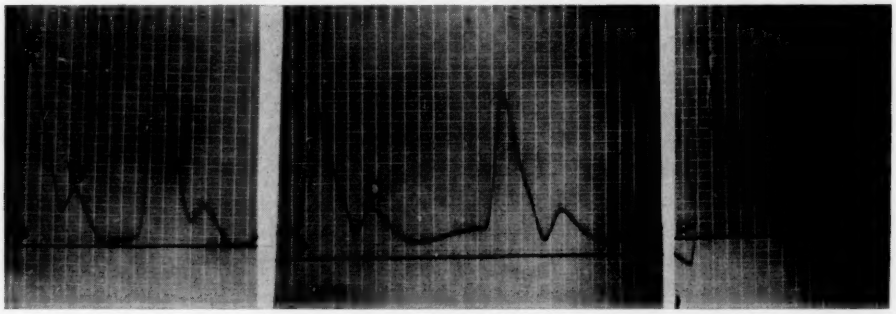

Fig. 2.—Normal arterial pulse waves from three healthy subjects. Note that the basic configuration remains the same although the dicrotic wave (*D*) may begin high or low on the descending limb of the initial wave (*I*). *P* is the applied cuff pressure at which the recording was made.

The ascending limb of the initial wave climbs steeply and has a somewhat less steep decline. In normal subjects, the initial wave reaches its peak within 0.1 to 0.15 second of the start of the wave. There is then a pronounced dicrotic wave which, in the finger, generally appears from 0.35 to 0.45 second after the start of the initial wave.

Fig. 2 illustrates tracings from the fingers of three other healthy human subjects. Tracings have been taken from the digits of 40 presumably normal

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human beings below the age of 40 (medical students, nurses, and other hospital personnel). Thirty-eight of the 40 have had tracings similar to these and have been classified as normal. In the two exceptions, the dicrotic wave was markedly diminished. In checking the history and background of these two exceptions, striking family histories of diabetes and coronary artery disease have been found. Illustrative is the record (Fig. 3) from one of these cases, a 23-year-old male medical student who had an abnormal finger tracing. Although the subject was normotensive and in good health, his mother was a severe diabetic who had had a cardiac infarction, and the student himself had recently undergone a glucose tolerance test which was interpreted as borderline diabetic. Although there is no histologic proof, the data at least suggest that the abnormalities on the Vasculogram may be related to changes in his peripheral circulation.

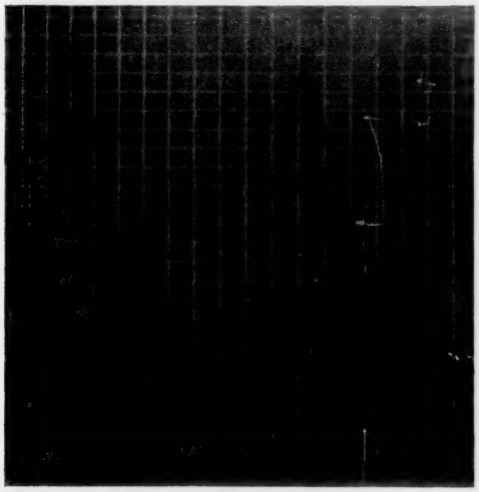
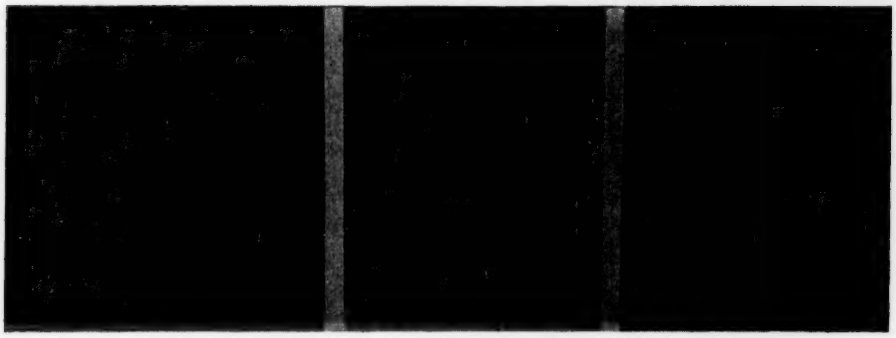


Fig. 3.—Abnormal arterial pulse waves recorded from the digit of a 23-year-old male medical student with a family history of diabetes and arteriosclerosis. The patient had a borderline glucose tolerance test. There was no clinical evidence of arteriosclerosis. Note the markedly diminished dicrotic wave (*D*).

The other exception was an abnormal finger Vasculogram in a 22-year-old presumably healthy male hospital employee. Although the subject had no clinically detectable evidence of arteriosclerosis, both parents had succumbed to cardiac infarction at an early age.

Tracings taken on the same subject many months apart show no significant differences. An example is the case of J.L. (Fig. 4), a healthy 22-year-old man, whose tracings were repeated over a nine-month period. The good reproducibility shown in this case is characteristic of normal healthy subjects. In this case and in others, varying conditions of room temperature and position of the limb did not alter the configuration of the pulse wave.

A new model of the instrument which substitutes a Statham strain gauge system for the piezo-electric crystal has given similar records in preliminary studies. Fig. 5 depicts a piezo-electric crystal recording and a strain gauge recording taken within a few minutes of each other from the same digit of the same subject.



November, 1951 March, 1953 July, 1953

Fig. 4.—Three tracings over a nine-month period of time from the same digit of a healthy young man. Note the similarity of the recordings.

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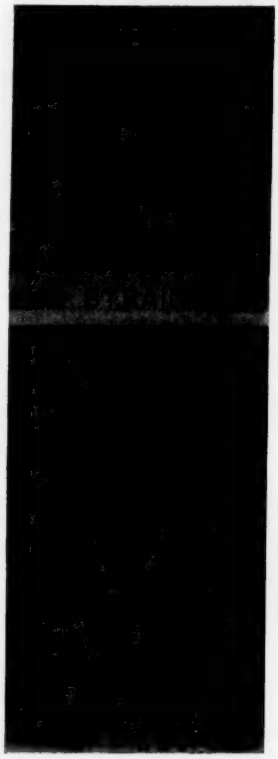

Fig. 5.—Comparison of strain gauge system recording and piezo-electric crystal recording taken within a few minutes of each other from the same digit of the same patient. The initial wave (*I*) and the dicrotic wave (*D*) components of the pulse wave are independent of the pressure line (*P*). The vertical lines are time signals 0.1 second apart and the horizontal lines represent pressure increments of 10 mm. Hg. in the periarterial recording cuff. The applied pressure in these two examples is 68 mm. Hg. Note the similarity of the pulse wave form in both recording techniques.

COMPARISON OF INTRA- AND PERI-ARTERIAL PULSE WAVES

All of the tracings described thus far were recorded form a cuff applied external to the limb or digit. Simultaneous intra- and peri-arterial pulse wave records have been taken in order to determine whether they are similar in configuration. The intra-arterial recordings were performed with the use of an 18 gauge 2 3/64 inch, No. 488LNR Cournand needle, transmitting pulse pressure waves to a Statham P-23A absolute pressure strain gauge. The peri-arterial recordings were taken by applying an air-filled 1½ by 3 inch sensitive rubber cuff externally to the examined artery about 1½ to 2 inches distant from the intra-arterial needle point. The external pulse waves were transmitted to a Statham P43-0.05D-350 differential pressure strain gauge. The recordings were made on a two-channel direct writer. Simultaneous tracings have been recorded from the brachial arteries of 5 presumably normal human subjects. In all cases the pulse waves measured by these two methods have been similar (Fig. 6).

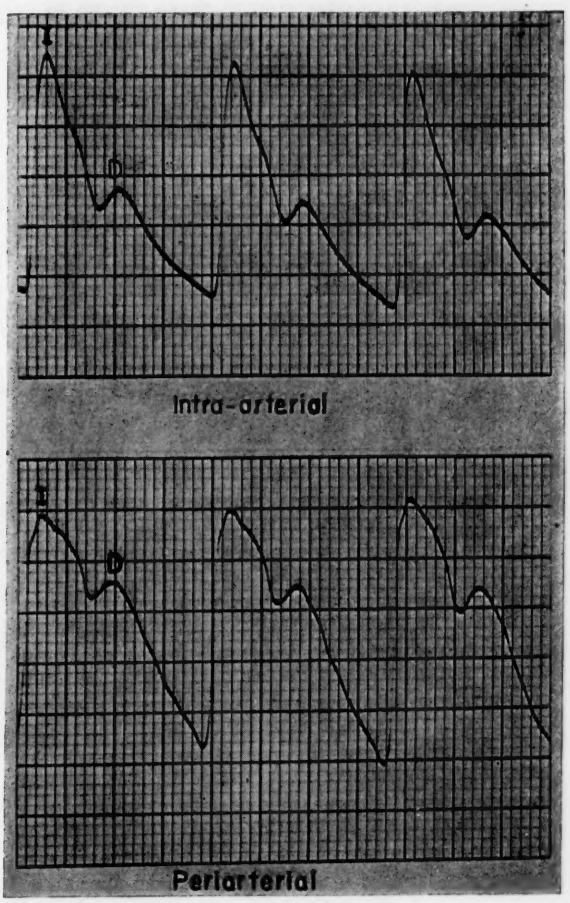

Fig. 6.—Simultaneous intra-arterial and periarterial pulse waves taken from a healthy 26-year-old woman. The tracings were recorded from the right brachial artery, using a two-channel direct writing strain gauge system. Note the similarity of the well-defined dicrotic wave (*D*) in both tracings. The slight difference in the form of the initial wave in the two tracings has been noted in other normal cases as well. The cause for this difference is not known.

Both the initial wave and the characteristic dicrotic wave are well defined on these normal subjects.

THE VASCULOGRAM IN HUMAN ARTERIOSCLEROSIS

In contrast to the normal tracings already seen is the record in Fig. 7 from the finger of a 62-year-old man with diabetes mellitus and documented coronary arteriosclerosis. The basic configuration of the arterial pulse wave has changed. The major difference noted in this instance of the disease is the absence of the dicrotic wave. Examples of various degrees of abnormality are shown in Fig. 8.

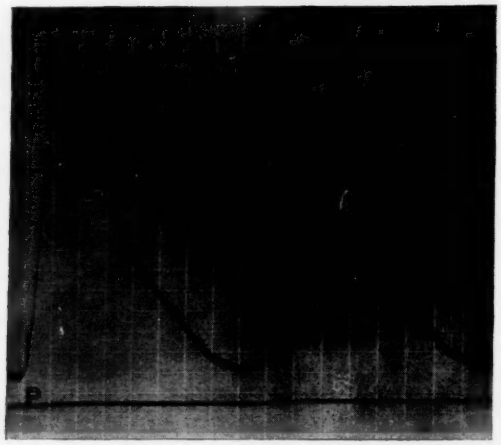

Fig. 7.—Arterial pulse waves from the digit of a 62-year-old man with diabetes mellitus and documented coronary arteriosclerosis. Note the complete absence of the dicrotic wave.

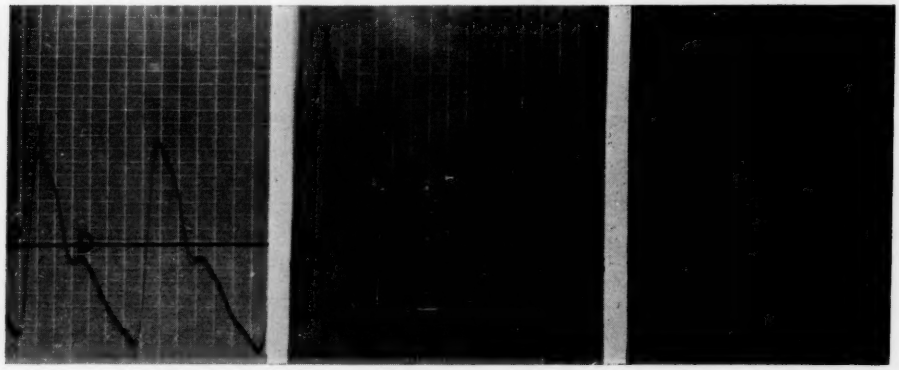

Fig. 8.—Examples of abnormal arterial pulse waves from the digits of 3 patients with clinical evidences of arteriosclerosis. Note the diminution to disappearance of the dicrotic wave (*D*). The pressure line (*P*) is recorded simultaneously with, but independently of, the components of the pulse wave. The position of the pulse wave on the paper is irrevelant to its form.

Consistently, the change is a diminution in the height of the dicrotic wave so that it may appear only as a thickened portion of the descending limb and may even disappear. An example of the reproducibility of tracings in abnormal human subjects in shown in Fig. 9.

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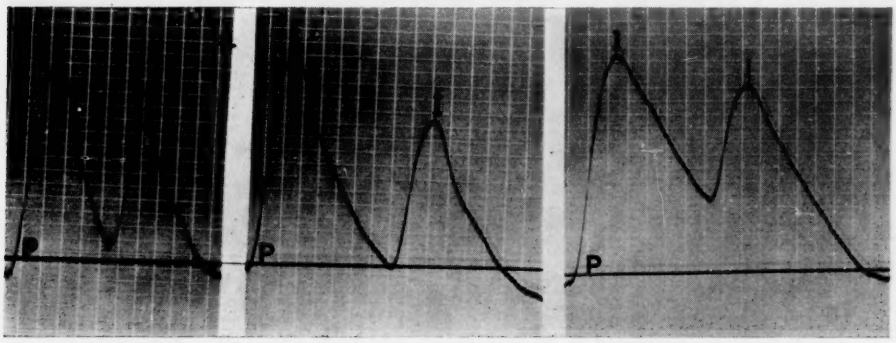
As in the normal subjects already described, recordings of the pulse wave taken from within the brachial artery of the 9 tested human subjects with clinical evidences of arteriosclerosis were similar in configuration to the simultaneous cuff recordings. Fig. 10 shows the tracings in two such cases. Consistently, in the arteriosclerotic group, the dicrotic wave was diminished or absent both inside and outside the vessel.



July, 1952 November, 1952 December, 1952

Fig. 9.—Three tracings over a six-month period of time from the same digit of a 70-year-old man with advanced generalized arteriosclerosis. Note the absence of the dicrotic wave in all tracings. The cardiac rhythm is that of auricular fibrillation.

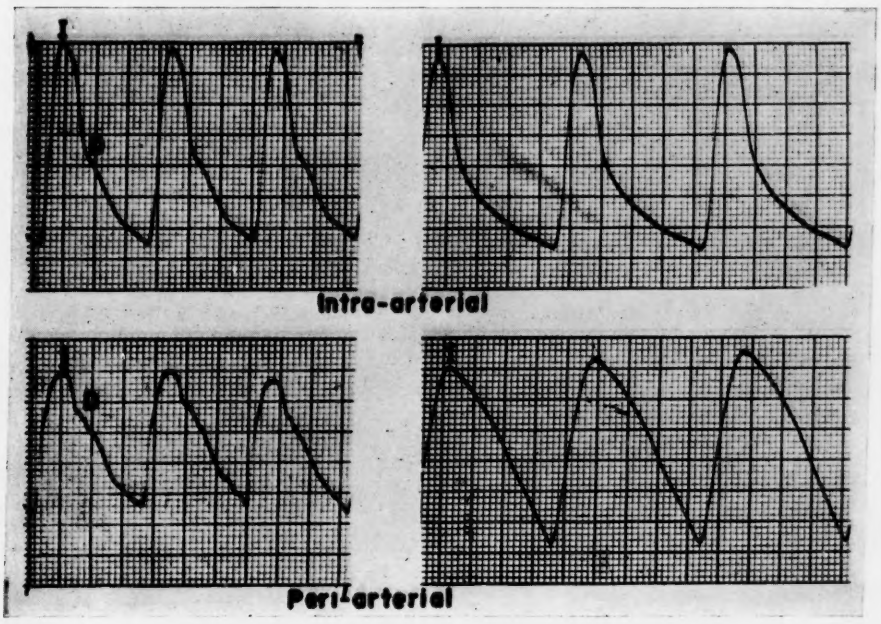


Fig. 10.—Simultaneous intra-arterial and periarterial pulse wave tracings from two cases with clinical evidences of arteriosclerosis. The tracings were recorded from the right brachial artery using a two-channel direct writing strain gauge system. Note the marked decrease in the dicrotic wave (*D*) in the first case and its complete absence in the second case. In the second case the periarterial recording cuff was distal to the intra-arterial needle point. The pressure in the periarterial recording cuff was below the patients' diastolic pressure level. The slight difference in form between the intra-arterial and periarterial pulse waves has been noted in all cases. The cause for this difference is not known.

The technique has now been used to study 122 hospitalized patients of various ages with myocardial infarction, generalized arteriosclerosis, diabetes mellitus, or hypertensive vascular disease, each of whom had clinical evidences of arteriosclerosis. One hundred and sixteen of these 122 (95 per cent) had abnormal tracings (Table I), the major change noted being a diminution to disappearance

TABLE I. ONE HUNDRED AND TWENTY-TWO HOSPITALIZED PATIENTS WITH DISEASES ASSOCIATED WITH CLINICAL ARTERIOSCLEROSIS (98 MALE, 24 FEMALE)

AGE (YR.)	DIABETES 16 M., 4 F.		HYPERTENSIVE VASCULAR DISEASE 15 M., 9 F.		CORONARY ARTERIOSCLEROSIS 42 M., 2 F.		GENERALIZED ARTERIOSCLEROSIS 25 M., 9 F.	
	VASCULOGRAM		VASCULOGRAM		VASCULOGRAM		VASCULOGRAM	
	NORM.	ABN.	NORM.	ABN.	NORM.	ABN.	NORM.	ABN.
10–19	0	1						
20–29	0	2	0	2				
30–39	0	2	0	3	1	1		
40–49	0	5	0	6	4	8	0	2
50–59	0	3	0	10	0	9	0	11
60–69	0	5	0	3	1	14	0	7
70–79	0	2	0	0	0	6	0	10
80–89							0	4
Total	0	20	0	24	6	38	0	34

of the dicrotic wave. An additional 68 hospitalized patients who were ill with other disease states and showed no clinical manifestations of arteriosclerosis were also studied. Fifty of the 68 (74 per cent) had normal finger pulse wave records (Table II).

TABLE II. SIXTY-EIGHT HOSPITALIZED PATIENTS WITHOUT CLINICAL EVIDENCES OF ARTERIOSCLEROSIS (59 MALE, 9 FEMALE)

AGE	NORMAL VASCULOGRAM	ABNORMAL VASCULOGRAM
10–19	11	0
20–29	11	0
30–39	6	3
40–49	12	4
50–59	8	8
60–69	1	1
70–79	1	2
Total	50	18

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DISCUSSION

The mode of origin and propagation of the dicrotic wave has been investigated for many years. The classic theory explains the dicrotic peak as a reflected wave initiated by the recoil of the arterial blood column against the closed aortic valve. The studies of Hamilton, Remington, and Dow,[1-4] Wiggers,[5] and Alexander[6] have shown that the form of the arterial pulse wave shows a progressive transformation in its passage down the aorta and peripheral arteries.

Despite evidence[1,2] that peripheral factors play a role in the formation of the distinctive waves seen in arterial pulse tracings, it may properly be said that, at present, the mechanism of origin of the dicrotic wave remains a subject for further investigation. It should be emphasized that this report describes only a series of empirical observations in a number of human cases without attempting to explain the mechanism of the dicrotic wave. These observations indicate that the dicrotic wave diminishes or disappears in the presence of clinical evidences of arteriosclerosis.

It is recognized that other factors, in addition to arteriosclerosis, may cause the dicrotic wave to diminish or disappear. It has been noted (Table I) that all 24 patients with hypertensive vascular disease, ranging in age from 20 to 69 years, had abnormal pulse wave tracings. This suggests that increased "tonus" of the vascular wall may abolish the dicrotic wave. It is proposed to study this further by testing the effect of norepinephrine infusions in normal subjects.

As pointed out earlier in this report, studies have been carried out in 2 patients apparently free of clinical arteriosclerosis who have abnormal arterial pulse wave tracings, both of whom have family histories suggesting a possible early tendency to abnormalities in their vessels. Pulse waves have also been recorded from the digits of five subjects with diabetes mellitus below the age of 40 (Table I). The tracings in these patients were abnormal although there were no clinical evidences of vascular disease. Finally, it has been noted that, with advancing age, the size of the dicrotic wave appears to diminish.

It is evident that in studies of human subjects one is limited by the same factors that make all studies of human arteriosclerosis so difficult—the lack of histologic proof in life, the irregular distribution of the lesions, and the likelihood that the "control" or "healthy" group contains individuals with arteriosclerosis. It is fully realized that the pulse wave recordings from peripheral arteries may bear no constant relation to what is taking place in the coronary or cerebral vessels.

There appear to be three methods of attempting to overcome these limitations in this study of human arteriosclerosis. The first method is to carry out a continuing, long-term, mass population survey and statistically to correlate the changes noted in the arterial pulse wave contour with the clinical development of vascular disease. The second is to study select patient groups where the incidence of vascular complications may reasonably be expected to be higher than usual. Such a group might be composed of young diabetic subjects and their families. Finally, a shift of emphasis from the human disease to a study of experimentally induced arteriosclerosis in the dog offers a means of correlating the periarterial pulse wave tracings with the actual pathology within the vessel. Such an experiment in the dog is already under way.

SUMMARY

1. A sensitive instrument for the recording of arterial pulse waves is described. It is tentatively designated as a Vasculograph.

2. The characteristics of the normal arterial pulse wave contour, as recorded by this instrument, are reported. The accuracy of the recordings has been demonstrated by the similarity of simultaneous intra- and extraarterial tracings.

3. The changes in configuration of the arterial pulse wave in the presence of clinical evidences of arteriosclerosis appear to be diminution to disappearance of the dicrotic wave. The accuracy of this finding has also been demonstrated by simultaneous intra- and extraarterial recordings.

4. The implications of the disappearance of the dicrotic wave in the presence of clinical evidences of arteriosclerosis are discussed.

We wish to express our appreciation to Professor Burton Erickson for his aid in the technical aspects of this project, and to Dr. Arthur R. Wertheim for his helpful advice and counsel, the Cambridge Instrument Co., Inc., and the Dorner Instrument Development Co., for the construction and technical development of the instruments.

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APPENDIX

Radial movements of the arterial walls occur predominantly in direct response to variations in blood pressure. An envelope of air made to encompass a short section of a limb or digit and caused to experience pressure is itself a measure of the pressure change. Certain attenuation must occur in the transmission of energy from the blood stream by this method, but accurate large

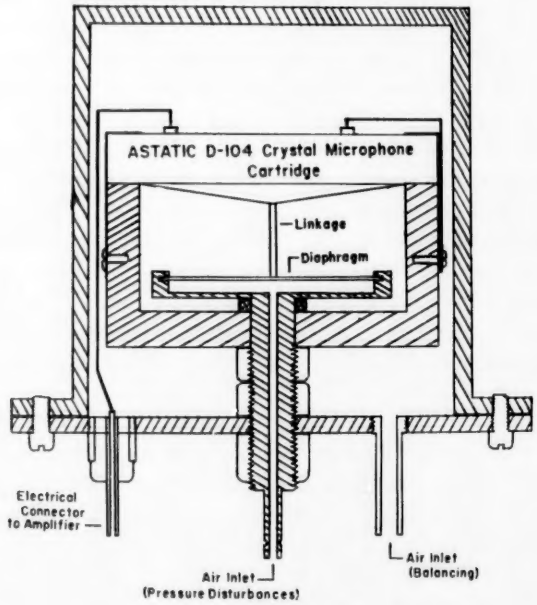
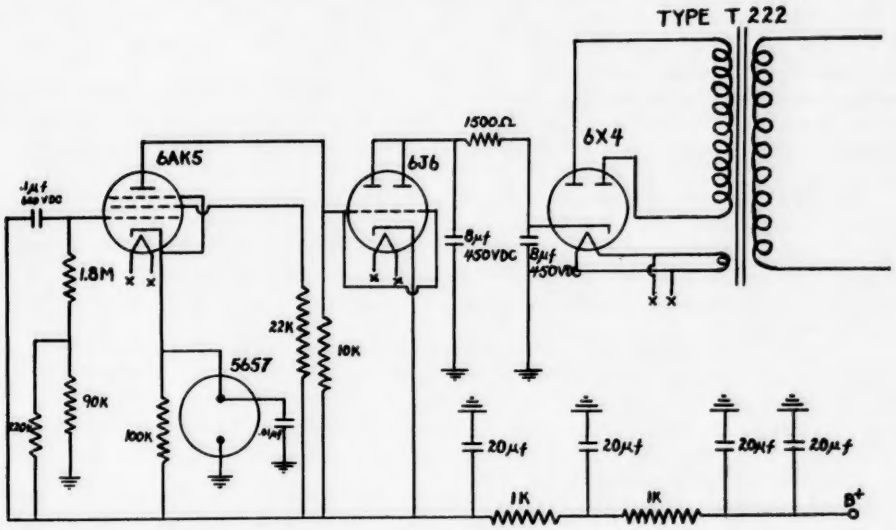
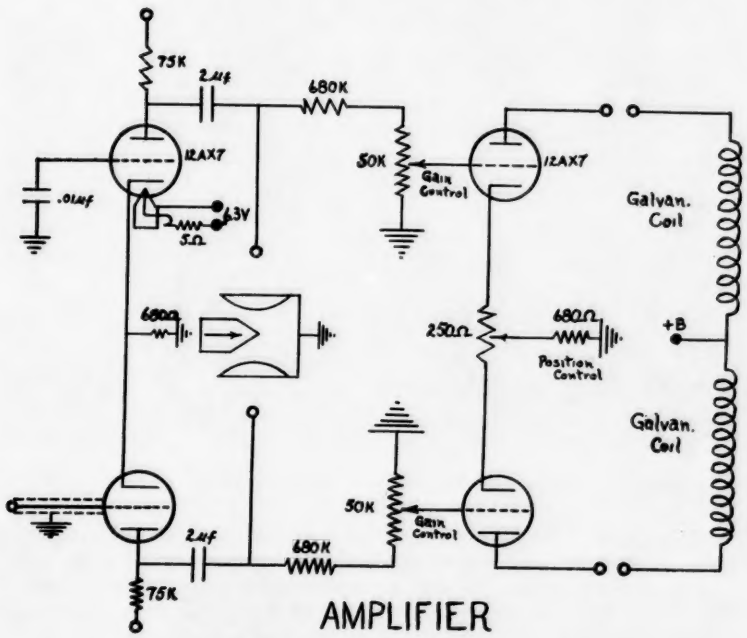


Fig. 11.—Differential pressure transducer.

scale recordings of the pressure change in the air envelope are sufficient to permit study of vascular conditions which alter the normal configuration so recorded. Minimum attenuation of energy transfer appears to occur at an external pressure level approximately that of the intra-arterial diastolic pressure.



POWER SUPPLY



AMPLIFIER

Fig. 12.—Electrical components of the Vasculograph.

A sensitive rubber cuff with an inelastic backing is applied to the external surface of the limb or digit. The cuff consists of a thin rectangular membrane 1½ by 3 inches, cemented at the edges to a backing piece of rubberized cloth. A ⅛ inch I.D. nipple attached at the center of the cloth is connected to a three foot length of ⅛ inch I.D. rubber tubing. This tubing serves the dual purpose of inflating the cuff and connecting it to the recording chamber of a differential pressure transducer. The cuff is attached by an inelastic strap to the extremity which is to be examined. This strap, slightly wider than the cuff itself, is held in place by a 9-inch Scudder foreceps.

The differential pressure transducer (Fig. 11) consists essentially of a circular beryllium copper diaphragm 0.006 inch thick, 1½ inches in diameter, separating two air chambers. Air pressure required to inflate the cuff is introduced to both chambers, causing no deflection of the diaphragm. Pressure disturbances originating at the cuff, however, are conducted to the recording chamber only. These disturbances cause the diaphragm to deflect according to their intensity and sign.

Deflections of the diaphragm are transmitted by mechanical linkage to a piezo-electric crystal cartridge which generates electrical energy according to the mechanical motion imposed upon it. The crystal unit (Astatic microphone cartridge D-104) has an output of -45 db referred to 1 volt per micro bar. Output from the crystal is amplified using a Class A balanced push pull amplifier with continuous variable gain from 0 to 16 db max. The amplifier feeds a dual coil string type mirror galvanometer (Fig. 12).

Permanent recordings are made on 12 cm. wide ECG paper, using a Cambridge three-speed camera. Camera speeds are 12½, 25, or 50 mm. per second. Timing marks appear as equally spaced vertical lines.

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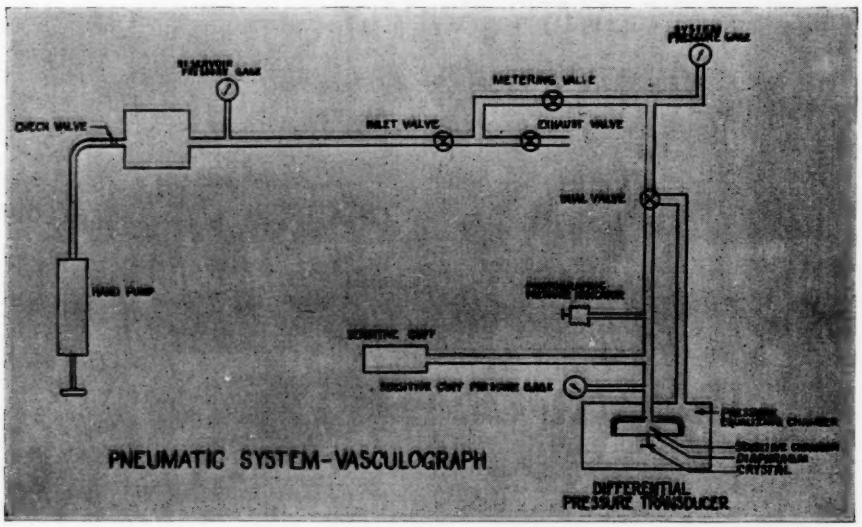

Fig. 13.—Schema of the Vasculograph pneumatic system.

Fig. 13 is a schematic diagram of the Vasculograph pneumatic system. An air reservoir contains air at 10-15 psi pressure. The inlet valve releases air from the reservoir to the system through a metering valve which controls the rate of supply. Air is introduced simultaneously to all parts of the system. A system pressure gauge and a cuff pressure gauge indicate pressure in the system and cuff, respectively, and a calibrated bellows directs a recording light beam to the camera so that a record of pressure elevation in the cuff is obtained on all permanent records. The dual valve isolates the recording chamber from the pressure equalizing chamber of the transducer when recordings are made at constant pressure.

Fig. 14 is a curve showing frequency response of the entire system from cuff to galvanometer. The response is substantially flat to 40 cps which is well above the 5 to 6 cycle range encountered in studying arterial pulse waves.

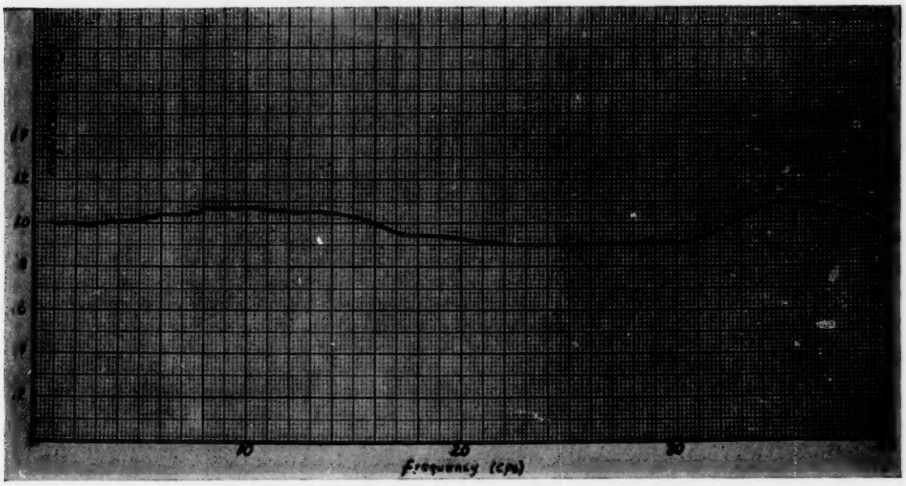

Fig. 14.—Frequency response curve of the complete recording system (Vasculograph).

Continuous variable gain control enables the operator to standardize the amplitude of recordings without affecting the configuration of the arterial pulse wave. This feature is of value in doing comparative studies over a period of time on the same subject. By recording at the same basic amplitude, it permits standardized conditions in so far as the instrument itself is concerned. The only variable will then lie with the patient.

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PARENT PARTICIPATION PROGRAM IN PEDIATRIC ONCOLOGY
A PRELIMINARY REPORT

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(Received for publication Nov. 10, 1955.)

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OF ALL the problems relating to the care of sick children, the personal care of children with neoplastic diseases has created intense emotional problems which have hitherto proved difficult to solve. In an effort to develop a more realistic and definitive program of individual management for these children, an intensive study of parental aid under professional supervision has been initiated at the City of Hope Medical Center.

Although the active participation of parents in the hospital care of their child may be novel in oncology, the parental care of sick children is far from revolutionary. The greater part of nursing sick children at home has been done by mothers since time immemorial. In most Asiatic and some African and European countries the family unity is traditionally maintained even in the hospital. Spence[1] employs the mother in the hospital to aid in the nursing of her child much as she would do at home, without active participation in the program. On the grounds of efficiency, necessity, and shortage of nurses, he suggested that in the future, more parental care of children in the hospital would be forthcoming. Orbach and co-workers[2], from a psychologic point of view, recently recommended "permitting the mother to participate as much as possible in simple nursing procedures." Interestingly enough, Sheldon[3] has been engaged for some years in soliciting aid from relatives in the rest home care of the aged in Sunderland, England.

A careful evaluation of many factors in the total problem resulted in a plan to study and, if possible, to alleviate some of the unfavorable features of the problem. The parents appeared to be one of the major fulcrums around whom the program might revolve.

In recognition of the emotional needs of the parents, children, and family in the treatment of serious long-term illnesses, such as cancer or the leukemias, the team approach was extended to a study of parent-child relationships in the treat-

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ment and investigation of children with cancer or leukemia. The immediate objective of this program was to select and train one or both of the parents in the tasks of caring for the child, both in the hospital and at home; second, to determine the limits of medical care and parental responsibility under these circumstances; third, to study the reactions of the parents, child, and professional staff when the parents were drawn into the active treatment and care. The plan was entitled: Parent Participation Program, and was initiated in April, 1954.

PARENT PARTICIPATION PROGRAM

To implement this program the following routine was established:

Selection.—Initially, the program had been related exclusively to the leukemias. It became immediately apparent that the program was equally applicable to all forms of neoplastic disease. For the past eighteen months, all patients on the pediatric oncology service at this medical center have been in the study. The elimination of any child from such a program soon created difficulties which could not be surmounted except by making the program available to all on the Tumor Wing. In those instances in which the parents could not devote sufficient time in the program due to other essential commitments, their place was taken by other parents or the staff.

Screening.—Since the parental background and the current situation with each child differed greatly, each case was screened carefully to obtain the maximum information concerning the entire family to permit a better understanding of the child and parents and perhaps to aid in their integration into the program. Originally it was decided to exclude any parent in whom it was felt the emotional problem would be overwhelming. In the past eighteen months, not a single instance has presented itself. The decision to enter the program has been largely self-determined on the basis of physical availability with relationship to home problems, occupation, etc.

In one instance, the father of a leukemic child developed the prodromata of an acute psychosis. He was immediately removed from the scene and given psychiatric aid. There had been no suspicion of any psychiatic abnormality prior to his entry into the program and in retrospect none could be developed. The need for a careful psychiatric evaluation of all parents has become apparent.

Grandparents have had free access to the situation, without screening, upon approval of the parents. There have been no unfavorable reactions.

Only if both parents accept the rules unconditionally are they permitted to enroll in the program.

Orientation.—After thorough confirmation of the diagnosis, the parents were informed of the status of the child and the seriousness and prognosis of the illness. The aims, procedure, and the experimental nature of the program were carefully outlined. The difficulties that may be encountered were stressed. The prognosis and implications of the major findings were individualized in detail for each parent and the parents were assured that everything would be done to further the comfort of and benefit to their child. A short indoctrination course informed the parents of the various neoplastic illnesses they would encounter on

the service so that they would be better able to anticipate the course of the illness and perform their duties with more understanding. The indoctrination must be complete and required amplification in this program. Formal meetings were held in the afternoons and evenings to permit both parents to attend. All efforts were made to answer questions and instruct the parents on the diseases in which their children were involved. Most parents evinced great interest and benefited by way of a more objective approach to the problem. This instruction period was then discontinued. Within six months, as new parents entered the program, the desire and need for reinstating these talks became apparent. The parents were urged to discuss the program in operation and suggestions to improve the program were solicited.

Duties were also assigned for ancillary functions—those of obtaining adequate blood donors for transfusions, arranging transportation to and from the blood bank, etc. One or both parents were assigned to specific duties related to their child and possibly to other children who were without parents.

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Nursing.—The official authority for the work on the floor remained with the Head Pediatric Nurse. Close cooperation between the nurses and parents developed in this manner and the morale remained encouragingly high despite the periods of strain that frequently arose. The duties assigned to the parents consisted of feeding, bathing, cleaning, diaper-changing, entertaining, reading, and amusing the children. Semiprofessional tasks were assigned by the nurse in charge as the situation warranted. All medications and other professional duties were performed by the nursing staff and physicians, and the parents were asked to withdraw on appropriate occasions when treatments were to be performed.

When a child recovered sufficiently to go home, the parents continued their care at home, maintaining the continuity of treatment and the confidence of the child. The parents, now trained in the proper care of their child in the hospital, were able to carry on the program, with supervision, at home. The children were seen frequently during return visits to the Outpatient Clinic and the parents, who by now had become semiprofessional observers, were able to give a more lucid account of their child's behavior at home and their response to the various forms of treatment that were undertaken.

Notes on the children at home were initially solicited, but the contents soon proved the parents to be too emotionally concerned for any real measure of validity. Temperature records, however, proved accurate and were continued.

Group meetings with the parents were held regularly by the Chief Pediatric Nurse. The experience of sharing common problems with others appeared to enable the parents to adjust more comfortably to their children with deeper understanding.

Physicians.—The parents were taken frankly into the confidence of the physician and this relationship was maintained and indeed fostered throughout the entire course of management. More recently, the parents have been invited on rounds concerning their child.

In those neoplastic diseases beyond cure or effective therapy and in which experimental therapy was considered advisable, the parents were fully informed of the risks and difficulties involved. Consent for such studies was obtained from both parents in writing in all instances. The parents assisted the investigations with great enthusiasm whenever possible and with remarkable insight into the difficulties that were encountered. In this way the parents were continually informed and consequently realized the necessity for frequent studies and determinations. They proved eager to cooperate in any way whereby greater accuracy and value could be attained.

Research Team.—The hope that lies potentially in research has been the major bulwark in the program. Without research, the parents would have little to look forward to that is not already predetermined in the light of previous experience. The enthusiasm of the clinical investigators and the thorough scrutiny that accompanied the studies permeated the entire atmosphere surrounding the patient and consequently, it was felt, infected the parents. The sheer force of numbers of individuals interested in the patient buoyed up the parent in the psychologic as well as the practical sense. The clinical team was also employed as a research tool to gain further information about the psychologic variables involved.

Social Service.—The social service worker has played a key role in the program. The social service department has become intimately involved in the daily operation of the program and consequently, more than any other single professional group, was able to avert difficulties, guide the course, and solve those delicate problems which often loomed so formidable to the distraught parent. The understanding and empathy of the social service workers in cooperation with the nursing and other professional staff personnel built the morale to an envious high in what otherwise could easily have been a shambles of lost hope. The seemingly inexhaustible resourcefulness of the Social Service Department to deal with innumerable and varied problems in diverse fields proved a great source of comfort to both the parents and the staff.

The close relationship of the social service worker with the parents and the child helped to bridge the gap that so often existed between the layman and the profession. The translation of the aims of the program and the professional goals were often so much better presented by the social service worker that it became an integral part of the program. The warmth, clarity, and kindness of such a presentation was reciprocated many times over by the parents.

Schooling.—The daily functions of school were related to viability and the future of the child and also to the parent. To abandon purposeful learning was in effect telling the parent and child that there was no future, no hope, and only irresolute useless time. The child denied schooling could be likened to a patriot exiled within his country. For these and many other reasons a varied, yet well organized, school program was established for all children on the pediatric service who were able to attend. Combined class instruction proved difficult because of the age differences, yet they were thought to be of great value. Individual instruction was, however, more often the rule. The parents attended school, often

in the background, yet learning the techniques and content of the instruction so that they could assist between school periods. The handicaps of bedridden, ill children were soon overcome in large measure due to the engaging interest of the school teacher.

Because the educational goals required a different emphasis in each learning situation, a regular curriculum as such could not be developed. It served instead as a basis upon which to explore the particular intellectual interests of the child. Music, reading, arithmetic, vocabulary, and social studies (geography and history) were the most popular subjects. Writing was limited to the less ill children.

Occupational Therapy.—Instruction in creative art was a most effective tool in gaining the interest of the patients and parents. The challenge of making something manually brought the subject and the patient into direct relationship to life today and for the future. The skillful occupational therapists attempted to select the proper items and medium for construction which not only occupied the child gainfully but afforded a rewarding sense of satisfaction unattainable by other methods. This area of endeavor rapidly became a popular section of the program.

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Clinical Psychologist.—The psychologist worked closely with the Social Service Department and the psychiatrist in the Parent Participation Program. In most instances, these studies were in an exploratory stage, searching for common variables in a thoroughly mixed patient-parent population with a common situation—that of having a child facing inevitable death. Clarification of personality traits, anxiety, confusion, and other psychologic factors were constantly under surveillance by this team. Single and group sessions have been most revealing of emotions (of the parents toward the child, disease, professional staff, and other members of the family) that had been completely unanticipated. The solution of a surprisingly large number of these alleged or actual problems was largely due to this part of the team, resulting in prompt reward to parent and professional staff.

Group dynamics techniques were employed to facilitate communication between members of the clinical team and to develop a more integrated approach to the parents and children.

DISCUSSION

The duration of hospital stay for most children is short, in keeping with the usual short-term illnesses or procedures, e.g., infections, tonsillectomy, plastic repairs, etc. Nevertheless, when the moment arrives for parents to depart, the children usually express their fears and displeasure in a heart-rending episode despite the reassurance that all will be well. As a consequence of the brief visiting hours, moreover, parents have often complained that they would like to be with the children more during the hospital stay. In general, however, the parents have become accustomed to the classic practice with the rationalization that it is traditional and probably in the best interest of efficiency. With the realization that their child will soon return home from the hospital, parents have customarily accepted this enforced separation. Such has been the pattern in the majority of hospitals in this country.

The neoplastic diseases, however, present a more formidable problem in the parent-child relationship, particularly if the possibility of cure has passed. Once the parents have learned that their child has a fatal illness, the desire to spend as much time as possible with the child is irrepressible. This is indeed so true that frequently the physician is faced with an adamant refusal by the parents to hospitalize the child because of the inevitable separation. To add the separation of the child to the already overtaxed emotional framework of these parents, with the full realization that the child may not leave the hospital alive, may indeed be an overwhelming experience.

Occasionally this decision is manifested by an obstinate refusal to respond to medical advice, and even by open hostility to the profession. Many factors undoubtedly contribute toward the development of this hostility; in some instances the overwhelming anxiety of the parents as grafted upon a pre-existing emotional instability; in others it represents a reaction to the inadequacy of medical science to conquer the disease as yet. The complex emotional relationships existing between the child and parents in such a serious illness are magnified many fold both by the child and parents when the inevitable outcome becomes apparent, further contributing toward an ever increasing anxiety. The fear that their children will be unhappy in the hospital surroundings disturbs many parents and appears to account for their constant presence in the waiting rooms and corridors of the hospital, awaiting the moment visiting hours are announced. The extreme amount of concern that is engendered by the full realization of the seriousness of the illness emphasized by the emptiness of the home, frequently creates a variable, yet considerable, degree of frustration reflected by irritability and resentment on the part of the parents toward the hospital, the nurses, and occasionally the physician. The potpourri of emotional conflicts becomes increasingly more complex as the illness progresses and often, unfortunately, results in the decision to keep the child at home despite the insurmountable obstacle of inadequate facilities and trained care.

Children who enter an oncology service are not always critically ill and consequently require varying amounts of attention, much of which is not necessarily at the professional nursing level. These tasks involve: hand feeding, forcing of fluids, diaper changing, and other duties essential for the proper care of children who are weak, exhausted, and often bedridden. The task of keeping such children happy is time consuming and requires skill, versatility, and patience. Many of these children, although critically ill, are apparently greatly disturbed by being placed in a hospital atmosphere; perhaps fearful of physicians and nurses and in some instances deprived of the opportunity to lean securely upon their parents. The feeding, management, and entertainment of these seriously ill children by a strange individual is often a difficult task. It has been our experience that most parents can handle their own children with much greater ease and facility.

The parental observation of the child without careful briefing of the scientific aspects of the disease or treatment may create erroneous and often misleading impressions. Parents, who visit only during regular hours, see the child gradually failing. The parents are not usually present when treatments, consultations, and care are being instituted. With the difficulties of communication between

hospital physician and parents being what they are, the natural reaction of many parents is to assume that little is being done, that their child is being neglected, and that more could be accomplished if they went elsewhere.

In general, parental concern over the child's welfare is at least equally or more pressing in the neoplastic diseases than in most other childhood illnesses where recovery is assured. The apparent inactivity creates an overwhelming desire to do something more for the helpless child, and is reflected by the parents repeated queries of physicians, nurses, aides, and orderlies in an effort to uncover some facts about the future hope for their child. Frequent, persistent questioning of the physicians and nurses may become unpleasant, particularly when the experience confirms the inexorable course of the situation. This excessive questioning may eventually lead to frank dissatisfaction on the part of the parents with the progress of the disease and the child is frequently taken from the care of one physician and brought to another. A survey of twenty childhood leukemic situations revealed that at least 3 or 4 physicians had been consulted in the course of the illness. The parents of leukemic children usually exhaust most sources of help within a short period after the diagnosis is made. If the information they receive from each successive physician is bluntly and ineptly discouraging, the parents then turn to the less informed and eventually to the quasiprofessional field, gradually sifting down to frank charlatans and similar disreputable persons. Many of these parents develop a deep resentment toward the medical profession, often to the point of open hostility, not so much because of the inevitable fulfillment of the physician's prediction, but for the curt, unsympathetic dismissal of the problem by abject defeatism.

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The experience of the Parent Participation Program indicates that the parents cannot be limited merely to menial tasks. Their concern and interest literally forced them into the total structure of the program from which they could not be restricted.

The parents soon sensed they were gainfully employed in close cooperation with the hospital, physicians, and nurses in attacking their specific problems. The impression was gained that their anxieties, fears, and frustrations were ameliorated. The children similarly sensed the close cooperation of the parents with the physicians, resulting in a more ready rapport of the staff with the patient. The very presence of the parents on the floor, often with permission to assist in minor treatments of the child, soon convinced even the most skeptical parents that a great deal was being done in an effort to help.

As the inevitable terminal state developed it was gratifying to note the support that was offered by other parents who were willing to give no little of themselves to share and dilute the grief of the parent, yet at the same time realizing that some day, in the not too distant future, they too faced a similar ordeal.

It has been of interest to note the return of some parents to the Parent Participation Program meetings after a reasonable period following the death of their child, in a determined effort to continue with the program.

SUMMARY

A Parent Participation Program for the care of children ill with a neoplastic disease is described. The primary aim of the program has been to develop a team approach of professional personnel and parents in the care of the child afflicted with a long-term fatal illness. Studies of the Program after its initial eighteen months have defined some of the limits of medical care and parental responsibility that can be safely assigned and the experiences encountered have brought the problems more clearly into focus. The program is considered to be still in its infancy, and many avenues of improvement remain as yet unexplored. The aims of the program involve significant benefits to the patient, the parents, and the profession as well. The results observed to date indicate that these aims can be realized. Further reports of this program will be forthcoming as additional experience is gained.

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NEPHROSIS OF CHILDHOOD: STATISTICAL EVALUATION OF THE EFFECT OF ADRENOCORTICAL-ACTIVE THERAPY

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(Received for publication Nov. 11, 1955.)

WITH more than five years experience in the use of adrenocortical-active hormones for the treatment of childhood nephrosis, it should be possible to determine whether such treatment can appreciably alter the underlying disease. The fact that at least temporary relief of edema can be obtained has been well established for a long time.[1] We are presenting here an evaluation of our experience at Babies Hospital with respect to general clinical condition and of a much larger group experience submitted by cooperating physicians with respect to survival time. In spite of the fact that the effect of treatment on the clinical condition of the patient is important to the person dealing with the sick child, this cannot be measured as objectively as the effect of therapy on length of life. Consequently, in this presentation, more emphasis is placed on survival time.

CLINICAL EXPERIENCE WITH BABIES HOSPITAL PATIENTS

Many persons working with children with nephrosis have had the impression[2,3] that increasing utilization of adrenocortical-active hormones has kept the patients in a generally more comfortable state. In an effort to make such impressions less subjective and susceptible to statistical evaluation we have used an arbitrary system of scoring clinical status. We have evaluated the general well-being (without regard to final outcome) of each of our patients in the active phase of nephrosis every year during the period from September through May, from 1951 through 1955.* To be considered in the "active phase" a patient must have required at least 4 clinic visits during the nine-month period under consideration. A case with obviously irreversible renal damage, or one apparently "cured," was excluded when it became apparent that such a state had been

Presented at the Combined Pediatric Meetings, Quebec, June, 1955.

*The reason for the selection of this nine-month period was that we initially planned to test the efficacy of using the sedimentation rate as a guide for treatment (to be discussed). This mode of management was begun in Sept., 1954, and this analysis was made in May, 1955.

reached. Since an individual who continued to meet the criteria of being active without irreversible renal damage was included for each corresponding year, the groups of cases for the various calendar years are not necessarily made up of different patients.

The scoring system was applied to the following 4 features: (1) degree of edema, (2) degree of proteinuria, (3) degree of hematuria, and (4) severity of infections. A grade of *zero* was arbitrarily assigned if the finding was normal, *one* if there was moderate aberration, and *two* for severe aberration. Thus the worst possible score for a month for any patient was eight. Degree of azotemia was not graded since it was not clear how to weight it relative to the other features, and also measurements of the serum nonprotein nitrogen were relatively infrequent.

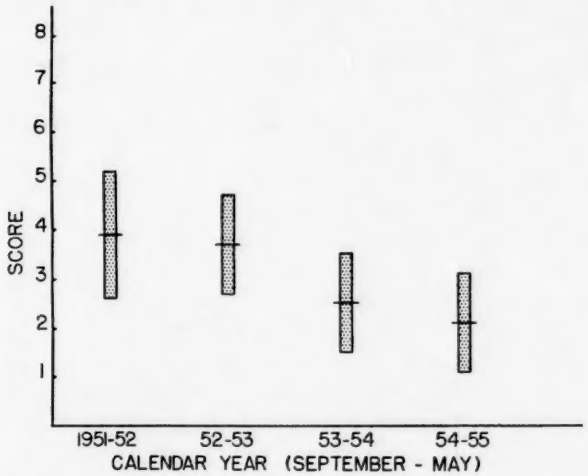

Fig. 1.—Clinical scores (mean ± 1 Standard Deviation) of patients with active nephrosis.

The available monthly scores for each individual during the calendar year were averaged to give his score for that year. The mean score for the group for that year was obtained by averaging all these individual scores. We felt that the process of averaging compensated to some extent for the crudeness of the scoring system. In Fig. 1 are seen the means and standard deviations of such scores of approximately 25 individuals for each year. Two facts are noteworthy: first, there is a steady reduction of mean score from year to year, progressing from 1951-52 when we used the hormones only to relieve edema, to subsequent years when we have been using them more and more intensively; second, the difference between the means of the first and the last years is highly significant (P is much less than 0.01).

Turning our attention to the number of "cures" produced, however, we found no cause for self-congratulation. Defining "cure" as the state of both being normal clinically and having normal laboratory findings for a minimum of six months, no change in the ratio of cures to deaths under the newer forms of management was evident.

If, instead of "cure," length of life after onset of edema is taken as the measurement of success in therapy, maintenance therapy seems promising. As first reported at the 1954 Nephrosis Conference,[3] our data suggested that in spite of the persistent proteinuria shown by many patients, we were at least prolonging life. Length of life here is measured from onset of edema, an event usually defined with considerable precision. In contrast, the onset of the disease cannot be so marked off because the pathologic condition may exist for an indefinite time before it becomes manifest.

COOPERATIVE STUDY OF SURVIVAL RATES*

When the report based on our relatively small number of cases followed at Babies Hospital was presented, other physicians with access to patients with nephrosis agreed to submit their data for statistical analysis. Preliminary reports of evaluations made before all the data were collected have been published previously.[1,4] The present report is based on 780 cases selected from over 1,300 examples of "the nephrotic syndrome" submitted by the physicians listed in Table I.

TABLE I

REPORTER	CITY
Barnett, H.	New York
Baxter, J. H.	Bethesda
Calcagno, P. L.	Buffalo
Cooke, R. E.	New Haven
Greenman, L.	Pittsburgh
Guild, H. G.	Baltimore
Heymann, W.	Cleveland
Kagan, B. M.	Chicago
Kohn, J.	New York
Kramer, B.	Brooklyn
Lange, K.	New York
McCall, M. F.	Montreal
McCrory, W. W.	Philadelphia
Merrill, A. J.	Atlanta
Metcoff, J.	Boston
Riley, C. M.	New York
Startzman, V.	Cleveland
West, C.	Cincinnati

The preliminary evaluations of this past clinical experience suggested that newer methods of management were prolonging life in children with nephrosis. Careful scrutiny of the data, however, showed that there were possible sources of bias, so that the results had to be considered far from decisive. Therefore, in the present report, great care has been taken to eliminate material which might conceivably introduce bias in favor of the treatment.

Of the some 1,300 cases submitted, the study includes all those which satisfy the following basic criteria:

*Supported in part by the National Nephrosis Foundation, Inc.

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1. Onset of edema before the twelfth birthday. This avoided the diagnostic confusion which may occur when adults develop the nephrotic syndrome, often secondary to known or unknown primary conditions.

2. Onset of edema in 1946 or later. This criterion was adopted to insure that only individuals having the opportunity for efficacious antibacterial therapy would be used, thus avoiding undue numbers of deaths due to infection.

3. Under observation by the reporting physician within six months after onset of edema. This insured a similarity of general supportive therapy, and more important, it insured a sample of patients seen early in the disease. General methods of supportive care in the hands of competent physicians could be assumed to be sufficiently similar to introduce no important bias.

The primary factor under study was the effect on survival of adrenocortical active hormone therapy (hereafter referred to as "hormone therapy"). Such treatment included the use of corticotropin, cortisone, or hydrocortisone. Modes of administration of these preparations are discussed under "Methods of Management." The hormone therapy given was classified in three categories: (1) no hormone treatment at all, (2) hormone therapy given sporadically only to relieve severe anasarca, and (3) hormone therapy given according to a preplanned schedule without regard to the presence or absence of edema.

Adequate comparison of these three types of management is impossible since, in the course of their illness, a large number of patients were subject to more than one such type. In addition, the decision as to type of treatment was frequently based on the prevailing clinical status of the patient: he might have been given hormone because his condition was so poor that a last heroic effort seemed justified, or, contrariwise, if he had lived with his disease for a long time without showing signs of significant renal damage, it may have seemed a reasonable risk to expose him to hormone therapy with the hope of finally inducing cure. Though started on hormone therapy he might have suffered interruption because renal function had deteriorated to the point of risk. Other examples could be cited of indeterminate indications for giving or for withholding hormone therapy.

In view of these difficulties we were led to present two comparisons: schedule-treated patients with all other patients; and a comparison of groups by calendar year of onset.

COMPARISON OF SCHEDULE-TREATED PATIENTS WITH ALL OTHER PATIENTS

In this comparison the first group consists of all patients who received scheduled treatment starting within the first six months after onset of edema. Within this period it is rarely possible to prognosticate whether the patient will go on to "cure" or to renal failure, so that such a group should be reasonably unselected with respect to severity. The second group consists of all other patients (untreated or "inadequately" treated) satisfying the basic criteria. It is evident that this latter group may contain some patients who were started on scheduled therapy at some time later than six months after onset, thereby making the benefits, if any, of scheduled therapy more difficult to detect.

It should be remarked that even this comparison is still subject to a possible bias. There is the rare patient in whom kidney damage progresses so rapidly that even in the first six months he reacts badly to hormone treatment with rising

nonprotein nitrogen and blood pressure. In such an individual one cannot start maintenance therapy and, therefore, he necessarily falls into the second group of inadequate treatment.

The survival rates as calculated by the modified life table method (see Appendix) are presented in Appendix Tables A and B, and in Fig. 2. Because of recency of observation, the number of cases in the schedule-treated group dwindles rapidly after thirty months following onset. At the thirty-month level the cumulative survival rates are 86.2 per cent for schedule treated and 72.0 per cent for the others. According to the significance test described in the Appendix, this difference is just barely significant (P is approximately 0.05).

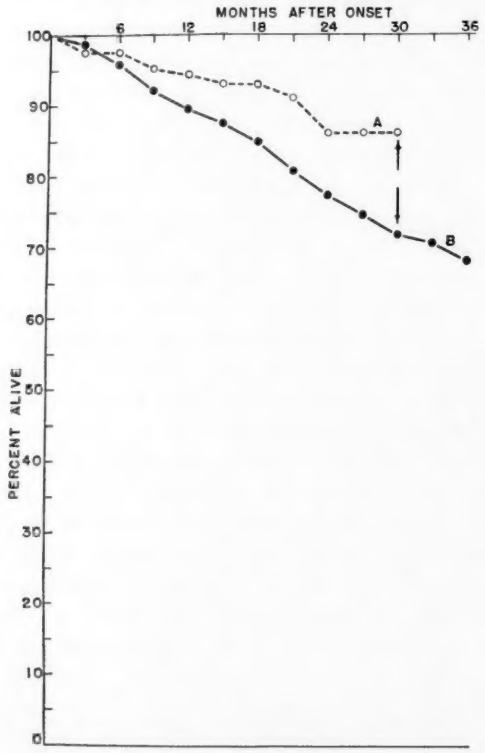

Fig. 2.—Survival curves of patients derived from Appendix Tables A and B. *A* represents patients started on scheduled treatment within six months after onset of edema. *B* represents all other patients seen by reporting doctor within six months after onset of edema.

COMPARISONS BY CALANDER YEAR OF ONSET

The possible bias mentioned in the previous comparison may be avoided by comparing survival curves of patients strictly on the basis of the calendar year of onset of their edema, regardless of the type of treatment they had, provided only that they fulfilled the basic criteria. A disadvantage of this comparison is that the mode of management changed only gradually throughout the period. Nevertheless, with the passage of time, more and more intensive therapy has been used, and so if treatment is effective, cases starting more recently should have better

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curves than earlier ones (since we do not feel that the disease itself has changed its character). Fig. 3 and Tables C and D show the result of this comparison. Those cases beginning in 1946 through 1950 had similar curves, and so have been pooled. In Fig. 3 the spread of their individual curves is indicated by the smoothed shaded area. It will be seen that the curves for those starting in 1951, 1952, and 1953 tend to lie above the earlier curves. At thirty-months the average cumulative survival rate for the years 1946-1950 was 69.8 per cent and for the years 1951-1953 was 78.0 per cent. This difference is just barely significant (P= 0.05).

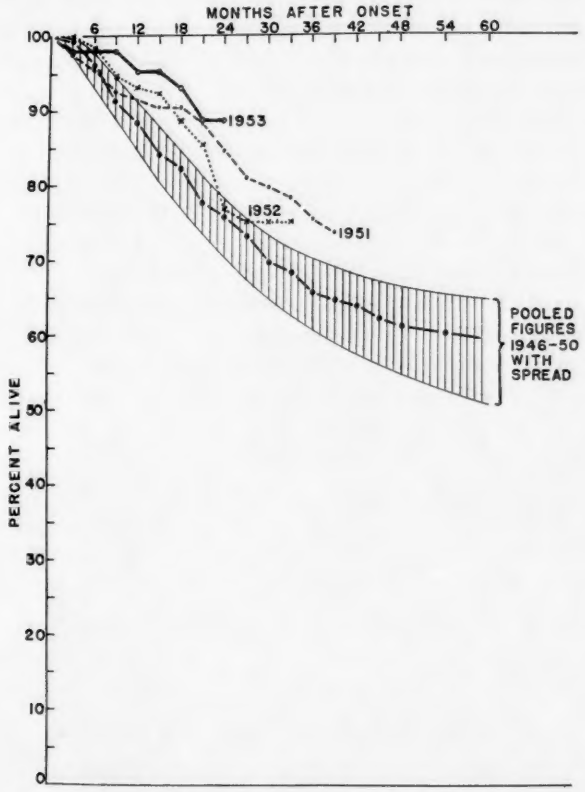

Fig. 3.—Survival curves of patients seen by reporting doctor within six months after onset of edema grouped according to calendar year of onset without regard to type of treatment. See Appendix Tables D and C.

METHODS OF MANAGEMENT

The types of preplanned schedules used by the various clinics fell into 5 categories. At the time the data were collected, the term "Maintenance Therapy" referred to several types: (1) large doses of hormone 3 consecutive days weekly,[5] (2) large doses of hormone 10 consecutive days monthly (our own modification, not yet formally reported), (3) large doses with low sodium, high potassium diet for 28 days consecutively,[2,3,6] (4) continuous treatment,[7] and (5) repetition of ten-day courses in rapid succession.[8] The groups managed on each of these schedules are too small to permit any valid comparison. Also, no data were available to permit comparison of the effectiveness of separate agents such as ACTH, cortisone, hydrocortisone, and the newer analogues.

At Babies Hospital, since September, 1954, and thus too recently to be included in the statistical evaluation, we have been using a new plan which has the advantage that it gives the physician the sense of directly controlling the situation rather than adhering blindly to a timed schedule, not knowing when it is safe to stop. This plan is based on the observation that the erythrocyte sedimentation rate, high in the edematous patient, falls with successful hormone therapy. In fact, it can be brought to normal, as a general rule, within four weeks of treatment, despite the fact that at the time of onset of diuresis it is usually still elevated. Accordingly, our current plan is to treat initially until this measurement is normal, though we have, in general, set an arbitrary maximum of 28 days. We have used ACTH, cortisone, and more recently, prednisone,* for this purpose. Thereafter, we consider any two of the three following factors as indications to start another course: (1) rising sedimentation rate, tested biweekly at first and less frequently as the situation becomes more stable, (2) increasing proteinuria, and (3) minimal traces of edema such as undue weight gain or parents' reports of puffiness of the eyes. With this system, used in the winter of 1954-1955, our mean score of clinical status of patients has remained about the same (perhaps a little better) than with previous types of treatment (Fig. 1). We have been able to show only a rough correlation of the sedimentation rate with other measurements such as total serum protein concentration, albumin/globulin ratio, cholesterol level and serum fibrinogen. We feel it is probably a composite measurement of several factors but is a useful and readily available clinical guide.

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SUMMARY

In summary, the evidence now available supports the belief that prolonged and intensive use of adrenocortical-active hormone therapy in childhood nephrosis not only improves the clinical status but also extends life. Only time will tell whether it will prove curative. We have suggested the use of the sedimentation rate as an added simple criterion to help decide when to give or withdraw such treatment.

APPENDIX

Statistical Methods and Tables of Survival Rates

Figs. 2 and 3 of the text are derived from modified life tables shown here in Tables A through D. The procedure follows essentially that outlined by Merrell and Shulman.[9] Column headings are explained as follows:

- x = time interval in months after onset of disease (edema). Figures given are inclusive; e.g.: 0 – 2 includes all time up to three months and so represents a three-month span.
- l_x = number of patients alive and under observation at beginning of interval x.
- n_x = number of patients first coming under observation during interval x. (Because of the criteria used in selecting patients there are no entries after six months.)
- w_x = number of patients withdrawing from observation during interval x for reasons other than death, such as loss to follow-up or recency of onset of edema.
- d_x = number of deaths during interval x.
- q_x = probability (expressed as per cent) of a patient's dying during interval x.
- S_x = cumulative per cent surviving to *beginning* of interval x.

*Meticorten, generously supplied by the Schering Corporation.

Since no patient came under observation at zero time from onset of edema, l_x is zero for the first three-month interval. Those under observation at the beginning of the next and subsequent intervals were calculated as:

$$l_{x+1} = l_x + n_x - w_x - d_x$$

The probability of dying (q_x) for all but the first three-month intervals was calculated as:

$$q_x = \frac{d_x}{l_x + \frac{1}{2}n_x - \frac{1}{2}w_x}$$

(After six months, n_x is, of course, zero.) This formula is based on the assumption that entries and withdrawals occur uniformly throughout the time interval so that, on the average, they can be considered to have been exposed to the risk of death for only one half of the interval.

Because of the large number of entries within the first three months, it seemed advisable to calculate the number of "effective exposures" from the entries (n_0, n_1, n_2) and withdrawals (w_0, w_1, w_2) for the individual months involved by using the following formula:

$$[(2.5\ n_0 + 1.5\ n_1 + 0.5\ n_2) - (2.5\ w_0 + 1.5\ w_1 + 0.5\ w_2)] \div 3$$

The probability of a patient dying during the first three months after onset of edema is then obtained by dividing the number of deaths in the three-month interval by this estimate of the number of effective exposures.

The probability of dying could have been calculated more easily if the cases had been dated from diagnosis instead of from onset of edema, thus eliminating the need for the column of entries (n_x). We preferred not to do this because of the possible difference between a patient one month after onset of edema and another five months after onset. Restricting the group to those observed within three months of edema would have obviated some of these difficulties but the number of patients would have been greatly diminished.

The cumulative survival rate (S_x) is obtained as the product of the probabilities of surviving during each of the preceding intervals, and these latter, of course, are the complements of the corresponding q_x.

A number of significance tests suggest themselves on intuitive grounds for comparing two cumulative survival curves obtained by the modified life table method. We decided to compare the survival rates at thirty months although this may not represent a complete comparison of the two survival curves. It was expedient to compare the logarithms (to the base 10) of the survival rates, using, as the standard error of the difference, the following modification of Greenwood's formula.[10]

$$\text{S.E.}_{(\log S_1 - \log S_2)} = 0.434\sqrt{\text{Sum of } \frac{q_x}{1 - q_x}\left(\frac{1}{E_{1x}} + \frac{1}{E_{2x}}\right)}$$

The sum extends over all intervals up to thirty months, q_x is the probability of dying obtained for the interval x computed from the two groups combined. E_{1x} is the number of "effective exposures" in interval x for the first group and similarly for E_{2x}. Thus, for the interval six to eight months from Tables A and B:

$$q_x = \frac{3 + 20}{131 - \frac{1}{2}(20) + 520 - \frac{1}{2}(27)} = 3.67\%$$

$$E_{1x} = 131 - \tfrac{1}{2}(20) = 121$$
$$E_{2x} = 520 - \tfrac{1}{2}(27) = 506.5$$

$$\frac{q_x}{1 - q_x}\left(\frac{1}{E_{1x}} + \frac{1}{E_{2x}}\right) = \frac{3.67}{96.33}\left(\frac{1}{121} + \frac{1}{506.5}\right) = .000391$$

Proceeding similarly for the other intervals, summing, taking the square root, and multiplying by the factor $\log_{10}e = 0.434$, we have: S.E. $_{diff.} = 0.0392$. Since the two thirty-month survival rates are 86.2% (S_1) and 72.0% (S_2), the difference in their logarithms is 0.0782, which is 1.99 times its standard error. This corresponds to a P of about 0.05.

TABLE A. PATIENTS RECEIVING HORMONE TREATMENT ON PREPLANNED SCHEDULE WITHIN FIRST SIX MONTHS AFTER ONSET OF EDEMA (ONSET OF EDEMA 1946-1954)

x (MONTHS)	l_x	n_x	w_x	d_x	q_x	S_x
(0)		(18)	(0)			
0–2 (1)		102(43)	6(3)	1	2.42	100.0
(2)		(41)	(3)			
3–5	95	54	18	0	0.00	97.6
6–8	131		20	3	2.48	97.6
9–11	108		18	1	1.01	95.2
12–14	89		14	1	1.22	94.2
15–17	74		22	0	0.00	93.1
18–20	52		8	1	2.08	93.1
21–23	43		12	2	5.41	91.1
24–26	29		8	0	0.00	86.2
27–29	21		4	0	0.00	86.2
30+	17		15	2		86.2

TABLE B. ALL PATIENTS SEEN WITHIN SIX MONTHS OF ONSET OF EDEMA, WITH NO SCHEDULED TREATMENT BEFORE SIX MONTHS AFTER ONSET (ONSET OF EDEMA 1946-1954)

x (MONTHS)	l_x	n_x	w_x	d_x	q_x	S_x
(0)		(213)	(5)			
0–2 (1)		460(159)	41(20)	3	1.18	100.0
(2)		(88)	(16)			
3–5	416	164	46	14	2.95	98.8
6–8	520		27	20	3.95	95.9
9–11	473		20	12	2.59	92.1
12–14	441		21	10	2.32	89.7
15–17	410		24	12	3.02	87.6
18–20	374		34	17	4.76	85.0
21–23	323		17	13	4.13	80.9
24–26	293		19	10	3.53	77.6
27–29	264		13	10	3.88	74.9
30–32	241		12	4	1.70	72.0
33–35	225		13	8	3.66	70.7
36–38	204		22	3	1.55	68.2
39–41	179		17	4	2.35	67.1
42–44	158		14	5	3.31	65.5
45–47	139		8	2	1.53	63.3
48–53	129		30	2	1.75	62.4
54–59	97		18	1	1.14	61.3
60+	78		72	6		60.6

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TABLE C. ALL PATIENTS WHOSE EDEMA HAD ITS ONSET IN THE YEARS 1946-1950, AND WHO WERE SEEN WITHIN SIX MONTHS AFTER ONSET, REGARDLESS OF TYPE OF TREATMENT

x (MONTHS)	l_x	n_x	w_x	d_x	q_x	S_x
(0)		(121)	(4)			
0–2 (1)		252(85)	27(15)	1	0.70	100.0
(2)		(46)	(8)			
3–5	224	86	27	8	3.16	99.3
6–8	275		8	14	5.17	96.2
9–11	253		5	8	3.19	91.2
12–14	240		4	11	4.62	88.3
15–17	225		3	5	2.24	84.2
18–20	217		3	12	5.57	82.3
21–23	202		5	5	2.51	77.7
24–26	192		1	6	3.15	75.8
27–29	185		2	9	4.89	73.4
30–32	174		1	3	1.73	69.8
33–35	170		2	7	4.14	68.6
36–38	161		8	2	1.27	65.8
39–41	151		2	2	1.33	64.9
42–44	147		6	4	2.78	64.1
45–47	137		5	2	1.49	62.3
48–53	130		30	2	1.74	61.3
54–59	98		19	1	1.13	60.3
60+	78		72	6		59.6

TABLE D. ALL PATIENTS WHOSE EDEMA HAD ITS ONSET IN THE YEARS 1951-1953 AND WHO WERE SEEN WITHIN SIX MONTHS AFTER ONSET, REGARDLESS OF TYPE OF TREATMENT

x (MONTHS)	l_x	n_x	w_x	d_x	q_x	S_x
(0)		(116)	(1)	(0)		
0–2 (1)		266(99)	10(4)	2(1)	1.32	100.0
(2)		(51)	(5)	(1)		
3–5	254	90	7	3	1.03	98.7
6–8	334		12	8	2.44	97.6
9–11	314		17	5	1.64	95.2
12–14	292		30	2	0.72	93.7
15–17	260		42	6	2.51	93.1
18–20	212		38	6	3.11	90.8
21–23	168		26	11	7.10	87.9
24–26	131		28	4	3.42	81.7
27–29	99		15	1	1.09	78.9
30+	83		75	8		78.0

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Editorials

MEDICAL RESEARCH—A MEDICAL SPECIALTY?

With the increasing availability of funds and facilities for medical research, an ever-growing number of younger physicians are being attracted into a career of full-time medical investigation. This selection of research as a full-time job may, for a given individual, be temporary, lasting only a few years, or it may endure for the active professional life of the physician. It is the purpose of this discussion to consider the actual as well as the ideal preparation for a research career currently afforded to the young physicians who elect medical research as a major field of professional endeavor.

The degree of Doctor of Philosophy in the scientific disciplines is a time-tested introduction to laboratory research. While striving for this degree, the candidate must, it is true, master the results of the research of others. A major part of his time and effort, however, is directed to a study of the day by day conduct of research. He takes courses in the several techniques which relate to his discipline, he learns how to synthesize and analyze, to isolate and identify, to procure, construct, measure and treat measurements mathematically, these being some of the operations of which laboratory research is comprised. Under guidance of an experienced investigator, he conducts and completes a research program in which many or all of these techniques may play a part. He receives instruction in the preparation and presentation of the results of his research in a manner acceptable to the scientific fraternity. Upon the completion of this course of training, in many cases, he may feel that his experience in research is still incomplete, and with the aid of a postdoctoral research fellowship, may secure, in another laboratory, still further and diverse training before launching into independent investigation.

The contrast between this background and that of most younger physicians is striking in a number of regards. The immense demands of the medical school curriculum make it very difficult to devote much time or attention to the work-aday conduct of research. True, an increasing number of medical schools are devoting time and effort to the introduction of the student body into the research laboratory. This, however, is usually limited to one-third or one-half of an academic year sandwiched into an otherwise exhausting schedule. Much of what is presented to the medical student is necessarily in the form of *Conclusions* of research projects of others, and but little attention can be devoted to the *Experimental* details upon which these conclusions are based. The student has

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very limited contact with the methods of research and must, for want of time, take it on faith that the conclusions presented are based upon sound experiments properly conducted.

Internship and residency training often adds but little to the physician's preparation for a research career. During these years he is likely to be very busy indeed with problems of patient care and it is the rare intern who manages to acquire much research experience. At the termination of such training, the young physician, if alert, may have hit upon a number of problems which he may wish to study, yet may have had little or no directed training in the methods of research which are the very essence of Ph. D. experience.

A century or more ago, it was a common event for an investigator to enter a successful career of research in a laboratory science without directed research training. With the growing body of knowledge and the increasing complexity of the tools and methods of laboratory investigation, this has become increasingly difficult until today it is very rare that major advances are achieved by investigators who are self-taught in research. The established and recognized path to a research career in the laboratory is via the Ph.D. or equivalent degree.

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What then is the clinician to do if he desires to make research his major life work? Without further specific training he may follow one of three routes. (a) He may restrict his research interests to encompass only such problems as he can handle with his presumably limited research skills. If he does this he is likely to find himself outstripped by competitors more advanced than he is in the mastery of modern tools and methods. (b) Taking advantage of the liberal grants programs he may hire investigators whose specific skills are profitably employed in his research program. This is at best a hazardous procedure in that the physician, who, as the grant applicant is necessarily the "responsible investigator," must assume responsibility for the work of specialists in areas other than his own, his understanding of which is at best imperfect. (c) Lastly, he may collaborate with independent specialists in remote research disciplines, thereby sharing the responsibility for published results with other qualified experts. This last device, perhaps the most satisfactory of the three, suffers from the disadvantage that, to a greater or lesser degree, the physician loses control of his own research program.

An alternative solution is based upon the candid recognition that medical research has become a complex business, requiring, for its optimal prosecution, a wide variety of skills and talents. The best course of training toward research that has evolved to date is that which leads to the degree of Ph.D. in a department of one of our major universities. Whereas the second doctoral degree may be and usually is of little value to the physician, the type of training which this encompasses is of immeasurable value to the career medical investigator. It is not possible for the medical investigator to foresee all the disciplines which he may need before the expiration of his career, nor would it be possible for him to school himself in all of these at the outset. This restriction is, however, equally applicable to the chemist or physicist. Certain basic disciplines and attitudes toward research can be taught, and can be readily learned in a suitable research environment.

It is therefore urged that each younger clinician who is drawn toward research as a life work give serious consideration to further education in research. Many opportunities for such education present themselves in some of the clinical and most of the basic sciences departments of our medical schools, in our privately and publicly supported medical research institutes, and in certain of our outstanding hospitals. To devise an organic synthesis, to create an analytical procedure, to handle tissue cultures, to grow viruses, to design or modify electronic instruments, to employ chromatographic or isotope procedures, to subject data to mathematical analysis—these and others are all good things to do during such a training period. Perhaps most important is to live in a research environment, in daily contact with one or more mature and sophisticated investigators; to learn, by observing and by doing, what constitutes a good problem and what comprises a good solution to such a problem. It is visualized that if medical research is to keep abreast of the advances which are occurring in other areas of science, this will in large part be the responsibility of physicians who have consciously and deliberately elected to secure such training in research.

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PARALYSIS AGITANS

Paralysis agitans, first described by Sir James Parkinson in 1817, is a symptom complex which develops as the result of widespread, diffuse lesions in the basal ganglia of the brain. The cardinal symptoms are rigidity of the musculature, and tremor. Other manifestations include: masklike facies, dysarthria, stooped posture, abnormalities of the gait, slowness and poverty of movements, and diminution of associated movements; all of which can be attributed to the rigidity of the somatic musculature. In addition, there may be signs of dysfunction of the autonomic nervous system, such as hyperidrosis and oiliness of the skin.

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Paralysis agitans may follow injury to the nervous system by infection, carbon monoxide intoxication, metallic or other poisonings, cerebral arteriosclerosis, or trauma; and it may be a feature of heredodegenerative diseases, such as hepatolenticular degeneration. All of the above named conditions account for only a minute fraction of the cases which are seen at the present time. The great epidemic of encephalitis lethargica (von Economo's disease) was the cause of a large number of cases in the years between 1918 and 1930. A number of the patients affected with this disease, which was presumed to be due to a filtrable virus, developed paralysis agitans during the course of the acute illness; and in a much larger number the symptoms developed several months to many years later as a sequel of the encephalitis. It is doubtful, however, whether the paralysis agitans which develops in patients at the present time can be attributed to epidemic encephalitis. In the majority of the cases which are seen today the symptoms develop in previously healthy individuals without any obvious cause (so-called idiopathic paralysis agitans).

The pathologic changes in the nervous system are meager in comparison to the dramatic and disabling nature of the symptoms. It is agreed that paralysis agitans is the result of damage to the cell masses at the base of the cerebral hemisphere known as the basal ganglia. These include the thalamus, caudate nucleus, lenticular nucleus, the subthalamic nucleus, the substantia nigra, and the red nucleus. The pathologic changes in the basal ganglia are usually microscopic in nature. Gross atrophy of these structures is rare. In the early stage, the neurones have an excess of pigment. Later, these cells undergo degeneration and are replaced by glia.

A peculiar fact is that the symptoms of paralysis agitans usually occur when there are diffuse widespread changes in several or all of the various nuclei of the basal ganglia and that they are rarely seen when there is a single large lesion, such as a tumor, hemorrhage, or encephalomalacia, localized to one of these nuclei. This may be due to the fact that the characteristic symptoms of paralysis agitans do not develop when the corticospinal and corticobulbar tracts are injured. The paralysis resulting from injury to this projection system masks or prevents the development of the characteristic symptoms of dysfunction of the basal ganglia.

Some authors have attempted to classify the patient on the basis of the presumed etiology into three groups: postencephalitic, arteriosclerotic, and idiopathic. This division is an artificial one, because with rare exceptions it is not possible to distinguish these various types on the basis of clinical data and it is not always possible to distinguish between them from the pathologic findings.

The diffuse nature of the pathologic changes, the variety of the clinical symptoms, and lack of knowledge of the function of the basal ganglia, have made it difficult to explain the pathophysiology of the symptoms. Various theories have been advanced but none has been entirely satisfactory. One explanation considers the symptoms to be the result of a disturbance in a reverberating circuit which involves the basal ganglia, thalamus, and the cerebral cortex.

It has been postulated that the rididity of the muscles in paralysis agitans is related to damage to the substantia nigra, and the tremor to injury of the caudate and lenticular nuclei. Variations in the degree of tremor and rigidity in individual cases could thus be explained by a disproportion in the amount of damage to these nuclei. There is insufficient pathologic evidence, however, to support this hypothesis.

The diagnosis of paralysis agitans is made without difficulty in the well-advanced cases from the characteristic features of the disease. Difficulty may be encountered in the early stages before the appearance of tremor, stooped posture, and masklike facies. Clues toward the correct diagnosis may be obtained if the facial expression, frequency of blinking, and the gait are carefully observed. The muscles of the extremities and the trunk should be tested for cog wheel rigidity.

Characteristic of the symptoms of patients with paralysis agitans is their susceptibility to the influence of emotional stimuli. The symptoms are greatly intensified when the patients are under emotional tension, such as an appearance before an audience or when trying to "put across a big deal." Conversely, the symptoms may occasionally be greatly lessened by emotional crisis. In such situations, the patients may be able to perform activities of which they are usually entirely incapable.

Localization of the signs to one side of the body is not uncommon in the early stages and this may lead to a consideration of the possible presence of an intracranial tumor. Intracranial tumors may cause a general retardation of physical activity similar to that in paralysis agitans but they rarely produce the characteristic constellation of symptoms of paralysis agitans; namely, masked facies, alternating tremor, and cog wheel rigidity.

The clinical picture of paralysis agitans may appear in the course of hepatolenticular degeneration and other heredodegenerative diseases of the basal ganglia. These diagnoses should be considered when the symptoms appear in childhood or before the age of thirty years.

Senile tremor is differentiated from that of paralysis agitans by its predilection for the head. When the extremities are affected, the tremor is increased by volitional movements. In addition, rigidity is usually an inconspicuous feature or entirely absent.

Familial tremor is more rapid than that of paralysis agitans. The involuntary movements are of a lesser range and they are increased by voluntary movements. There is a family history of the condition and tremor is the only symptom.

The tremors of hyperthyroidism, dementia paralytica, acute alcoholism, and other poisonings are distinguished from those of paralysis agitans by their rapid rate and lesser amplitude.

Paralysis agitans may develop in patients with other diseases of the nervous system. It has been noted in patients with combined system disease, tabes dorsalis, and other conditions. It is considered by most authorities that these combinations are fortuitous and that there is no causal relationship.

Some authors attempt to differentiate between paralysis agitans, postencephalitic parkinsonism, and arteriosclerotic parkinsonism on the basis of the severity of the tremor and the rigidity. The presence of tics, spasm, torticollis, oculogyric crises, or respiratory disorders when present in association with the tremor and rigidity, are characteristic of the postencephalitic form of the disease. In the absence of these it is not possible to distinguish between postencephalitis parkinsonism and paralysis agitans. The onset of symptoms in old age in association with other signs and symptoms of cerebral arteriosclerosis points to the latter as a causative factor. As stated previously, however, this differential is a tenuous one and not always supported by the pathologic findings.

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The course of patients with paralysis agitans is subject to considerable variation. The advance of symptoms is fairly rapid in some cases but in the majority it extends over one or several decades. Ten, fifteen, or more years may pass before the incapacity is severe enough to prevent useful occupation. Death is usually the result of factors other than the disease itself. In spite of the dramatic appearance of the tremor, it is not as disabling to the patient as the rigidity of the muscles. When the muscles are excessively rigid, voluntary movements may be greatly impaired or impossible. The cessation of tremor on voluntary movement makes it possible for the patient to perform many of his usual activities if there is no significant rigidity of the muscles.

Treatment at the present time is entirely symptomatic. Various alkaloids of the belladonna root and synthetic compounds with physiologic action similar to that of atropine, all have some beneficial effect on the muscular rigidity and the tremor. The results in some patients are gratifying, but on the whole they are rather meager. Success, when attained, seems to be related in part to the enthusiasm of the physician and the confidence of the patient in the therapy.

The inadequate results of medical therapy have led to the introduction of operative procedures designed to injure various portions of the basal ganglia or their connections with the cortex or spinal cord. Operations have been performed at all levels from the spinal cord to the cerebral cortex. There is no good rationale for any of these operations. If it is assumed that the symptoms are due to a disturbance in the interchange between the basal ganglia and the cortex, further interference with this interchange is not likely to improve the situation. A decrease in the severity of the tremor or rigidity has been reported as a result of operative procedures at the spinal and cortical level. This improvement can

usually be traced to an impairment of function of the corticospinal connections with attendant paresis or minimal weakness of the affected extremities. When this weakness clears, the tremor and rigidity usually return. Recently, attempts have been made to destroy the globus pallidus or its efferent connections. The value of this type of operative procedure cannot be determined at the present time but the results seem more promising. In some cases tremor and rigidity have been abolished without producing any weakness.

In spite of the fact that we do not have any satisfactory therapy for patients with paralysis agitans, the outlook is by no means hopeless. The meagerness of the pathologic changes, even in relatively advanced cases, could be interpreted as indicating that the symptoms are due to a functional disturbance in the activity of the neurones of the basal ganglia. Further evidence to support this hypothesis is furnished by the fact that many of the clinical features of paralysis agitans can be produced by the administration of chlorpromazine or drugs of the rauwolfia group. These symptoms disappear when the drug is withdrawn.

If it can be established that paralysis agitans is due to a toxic or metabolic defect, a good possibility exists of discovering a treatment which would arrest the progress of the disease.

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Book Review

DIFFERENTIAL DIAGNOSIS. THE INTERPRETATION OF CLINICAL EVIDENCE. By A. McGehee Harvey, M.D., and James Bordley III, M.D. pp. 665; indexed. Philadelphia, 1955, W. B. Saunders Company. Price $11.00.

The book is really a collection of elegant and erudite clinical pathological conferences. It can be opened and read, beginning at any chapter, and laid away at will. It is lively and interesting, written from a point of view which has great merit. There is no attempt made to cover every disease, nor is there always an effort to dream up every disease that might be remotely concerned with the differential diagnosis of the case under discussion. This approach, therefore, relieves the stultifying dullness of the formal texts on this subject.

The cases are nicely grouped and the general discussions of each group are very enlightening. The choice of a specific symptom such as "Pain in the Chest" or a sign such as "Jaundice" or other common denominators such as "Sudden Death" for a focal point from which the discussion of the case proceeds is an especially happy one. And the "Unknown" cases at the end provide a very pleasant exercise for the curious, which might supplant crossword puzzles or "who dunits" until the material is exhausted with very beneficial results in the education of students of medicine.

Somehow I wish that the subtitle had been chosen as the main one. The present title has misled some persons to believe that the volume was similar in nature to say, "French's Differential Diagnosis." One need only purchase this book under such a delusion to find out how delightful the volume is.

J. Murray Steele

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Books Received

CATTLE AND MEN. By Charles Wayland Towne and Edward Norris Wentworth. Pp. 384; indexed. Norman, 1955, University of Oklahoma Press. Price $4.00.

WHY PATIENTS SEE DOCTORS. By Seymour Standish, Jr., Blair M. Bennett, Kathleen White, and L. E. Powers, M.D. Pp. 94; with 18 figures. Seattle, 1955, University of Washington Press. Price $2.50.

AN INVENTORY OF SOCIAL AND ECONOMIC RESEARCH IN HEALTH. Compiled by Frederick R. Strunk. 1955 Edition. Pp. 266; indexed. New York, 1955, Health Information Foundation.

DERMATOLOGIE DER MUNDHÖHLE UND DER MUNDUMGEBUNG. Von Priv.-Doz. Dr. A. Greither. Mit einem Geleitwort von Prof. Dr. W. Schönfeld. Pp. 262, with 191 figures. Stuttgart, Germany, 1955, Georg Thieme Verlag. Price $9.45.

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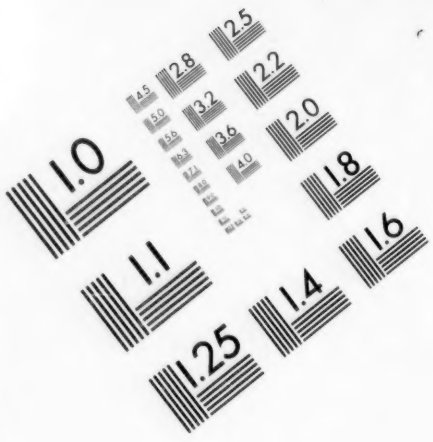

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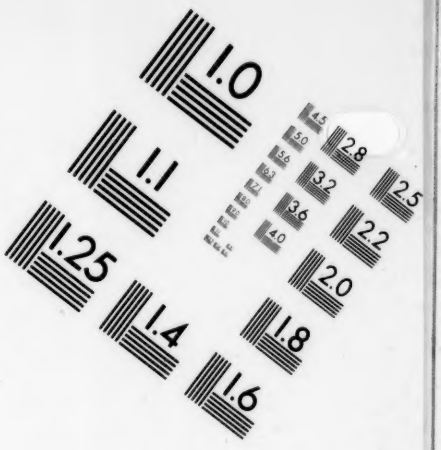

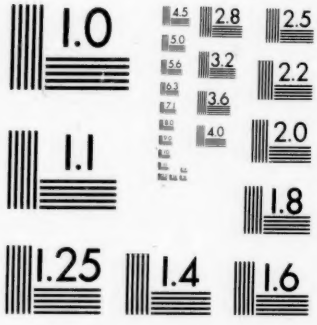

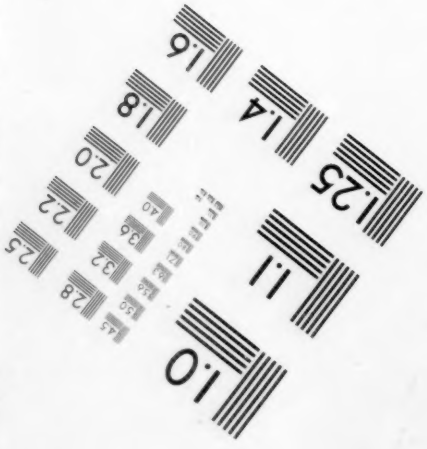

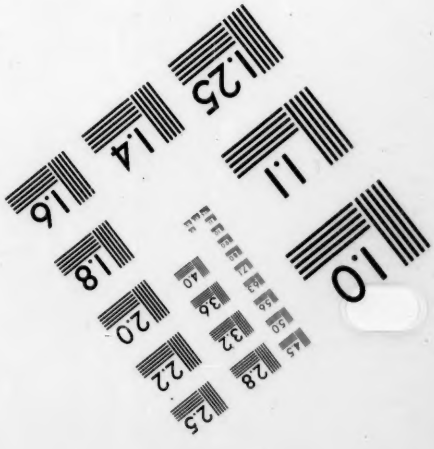

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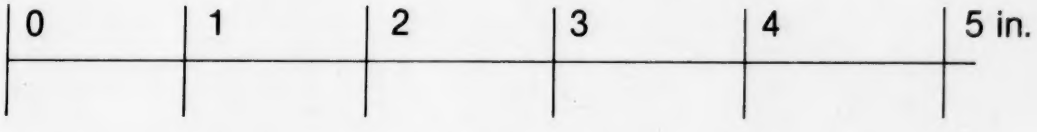

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